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BULLETIN OF
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NOTE ON A MECHANISM OF THE DISTRIBUTION OF WEALTH

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A population of individuals is considered to be characterized by a distribution of wealth which is the result of gain and loss from the outside as well as a result of exchange. The population is assumed to be uniform except for the variation in a parameter determining the manner of partition during exchange. The parameter is assumed to be normally distributed over the population. The resulting distribution of wealth is calculated for some special cases and it is found to be very asymmetric.

The mechanism of the distribution of wealth has been represented in terms of certain models (Marschak, 1943; Kalecki, 1945; cf. also Davis, 1948). The present representation is suggested from considerations of interacting neural nets (Landahl, 1947) which can account for some types of motivational interaction. However, rather than attempt to work out a detailed kinetics of interaction in these terms, we shall introduce simplifying assumptions.

We consider a large population of individuals who are all equal to each other except in their ability to gain or lose from an interaction. Let the individuals interact in pairs only and in such a manner that a fraction of the wealth of each is used in common during the interaction of mean duration τ. At the end of the time τ that part held in common is redivided in a manner which depends upon the magnitudes x_i and x_j of the abilities of each individual. We consider the contacts to be made at random in the population. In each case let equal amounts be contributed so that the amount is proportional to the wealth of the individual having the least. Let the division, at the end of the time τ, be carried out in such a manner that the gain of one at the expense of the other is in proportion to the difference between the values of the parameters x_i and x_j. Let W_i be the wealth of individual i who has a parameter x_i. Then when i interacts with j, such that $W_i < W_j$, the amount involved is $2\,\theta\,W_i$, θ being a constant fraction. The loss to individual i or gain to individual j is $\theta\,W_i\,\gamma(x_j - x_i)$ where γ is a constant which determines the effectiveness of a given difference in x. It is likely that a parameter of this type x will to a first approximation be distributed normally over the population. Thus if we define $p(x)$ by

$$p(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}x^2}, \quad \int_{-\infty}^{+\infty} p(x)\,dx = 1, \tag{1}$$

we may take $p(x)$ to be the distribution of x in the population. The units of x can be considered to have been absorbed into the quantity γ since only γx is ever required.

It should be noted that this linear approximation makes it mathematically possible for the loss to individual i to exceed his wealth. In order that this should not occur we must require $\theta\gamma(x_j - x_i) < 1$. However, if $\theta\gamma > 0.2$, the probability of this occurring would be less than one in several millions.

We shall only consider the case in which the interaction is a random process. Thus the net loss to individual i during one contact is on the average

$$\int_{x_i}^{\infty} \theta\gamma W_i(x_j - x_i)\,p(x_j)\,dx_j, \tag{2}$$

while his net gain, from individuals for which $x_i > x_j$, is

$$\int_{-\infty}^{x_i} \theta\gamma W_j(x_i - x_j)\,p(x_j)\,dx_j. \tag{3}$$

Let the rate of production of wealth by each individual be $P + AW(x) + Bx$ so that the production may be correlated with the wealth as well as the parameter x. We shall not consider anything beyond a linear approximation so that P, B and A are constants and $p > 0$. Let the rate of loss of wealth be given by $L + aW(x)$, where L represents a minimum requirement, and a is a positive constant. In an interval τ the net wealth of an individual changes from $W(x, t)$ to $W(x, t + \tau)$ so that the gain is $W(x, t + \tau) - W(x, t)$ or approximately $\tau\,\partial W(x, t)/\partial t$. To this extent we may then write (replacing x_i by x and x_j *by* x')

$$\begin{aligned} \theta\gamma \int_{-\infty}^{x} &(x - x')\,W(x', t)\,p(x')\,dx' \\ &+ \theta\gamma \int_{x}^{\infty} (x - x')\,W(x, t)\,p(x')\,dx' \\ + P\tau + A\tau W(x, t) + B\tau x - L\tau - a\tau W(x, t) &= \tau \frac{\partial}{\partial t} W(x, t). \end{aligned} \tag{4}$$

If we differentiate both sides of equation (4) with respect to x with t constant, we obtain

$$\begin{aligned}\int_{-\infty}^{x} W(x',t)\,p(x')\,dx' &+ W(x,t)\,z(x)\\ &+ W'(x,t)\,[xz(x)-p(x)-\alpha]\\ &+ B\tau' = \tau'\frac{\partial^2 W(x,t)}{\partial x\,\partial t},\end{aligned} \tag{5}$$

in which

$$\tau' = \tau/\theta\,\gamma; \tag{6}$$

$$\alpha = (a-A)\,\tau/\theta\,\gamma; \tag{7}$$

$$z(x) = \int_{x}^{\infty} p(x')\,dx', \tag{8}$$

and $W'(x, t)$ denotes the derivative with respect to x. In obtaining equation (5), we have used the identity $p(x)$ equals the integral of x' times $p(x')$ over the range x to infinity.

On differentiating again with respect to x, we obtain from equation (5)

$$[\alpha + p(x) - xz(x)]\frac{\partial^2 W}{\partial x^2} - 2z(x)\frac{\partial W}{\partial x} + \tau'\frac{\partial^3 W}{\partial x^2\,\partial t} = 0. \tag{9}$$

If we set $W(x, t) = U(x)V(t)$, then on substituting into equation (9) we obtain, on rearranging,

$$\{[\alpha + p(x) - xz(x)]\,U'' - 2z(x)\,U'\}/U'' = -\tau' V'/V = k, \tag{10}$$

in which U' and V' are derivatives with respect to x and t respectively. Since the first term is independent of t and the second is independent of x, they both must be equal to a constant which is here taken to be k. The equation with the first member of expression (10) set equal to k can be directly integrated since U is absent. The equation from the second member leads to an exponential. Thus the general solution for $W(x, t)$ can be written as sum of all such solutions $U(x)V(t)$, or, if M_k and N_k are arbitrary constants depending only on k,

$$W(x,t) = \sum_k \left[M_k + N_k \int_0^x \exp \int_0^\eta \frac{2z(\zeta)\,d\zeta}{\alpha - k + p(\zeta) - \zeta z(\zeta)}\,d\eta \right] e^{-kt/\tau'}. \tag{11}$$

We shall now consider only the steady state. The solution can then be obtained by setting $k = 0$ in equation (11). This can be more directly obtained from equation (10). From equation (11) it follows that $M_0 = W(0, \infty)$ and $N_0 = W'(0, \infty)$. Define $G_\alpha(x)$ as the integral which multiplies N_0 in equation (11). Note that $G(0) = 0$, $G'(0) = 1$. Thus for the steady state solution we have

$$W(x, \infty) = W(0, \infty) + W'(0, \infty) G_\alpha(x). \tag{12}$$

The solution of the differential equation must also satisfy equations (5) and (4). For the steady state the left-hand side of equation (5) vanishes for any x, so in particular for $x = 0$. Thus setting $x = 0$ and substituting $W(x, \infty)$ from equation (12) into (5) we find

$$\begin{aligned} W'(0, \infty) \int_{-\infty}^{0} G_\alpha(\zeta) p(\zeta) d\zeta + W(0, \infty) \\ - (.399 + \alpha) W'(0, \infty) + B_\tau' = 0. \end{aligned} \tag{13}$$

Similarly we obtain from equation (4) a second boundary condition:

$$\begin{aligned} W'(0, \infty) \int_{-\infty}^{0} \xi G_\alpha(\xi) p(\xi) d\xi - (P - L)_\tau' \\ + \alpha W(0, \infty) = 0. \end{aligned} \tag{14}$$

Since $G_\alpha(\xi)$ depends only upon α for a given ξ, those two equations may be solved to determine $W(0, \infty)$ and $W'(0, \infty)$ in terms of the parameters.

If we multiply through by $p(x) dx$ in equation (4) and integrate from $-\infty$ to ∞, then because of the cancelling of the time due to exchange, we obtain

$$(P - L) - (a - A) W_T = dW_T/dt, \tag{15}$$

where W_T is the total wealth, so that in this simple case the total varies with time according to

$$W_T(t) = W_T(0) e^{-(a-A)t} + \frac{P - L}{a - A} (1 - e^{-(a-A)t}). \tag{16}$$

It may be noted that the rate of income, I, may be defined as the sum of that which is produced and that which is gained by exchange. Thus we may write

$$I(x, t) = \frac{\partial W(x, t)}{\partial t} + L + aW(x, t). \tag{17}$$

For the steady state the income is a linear function of the wealth.

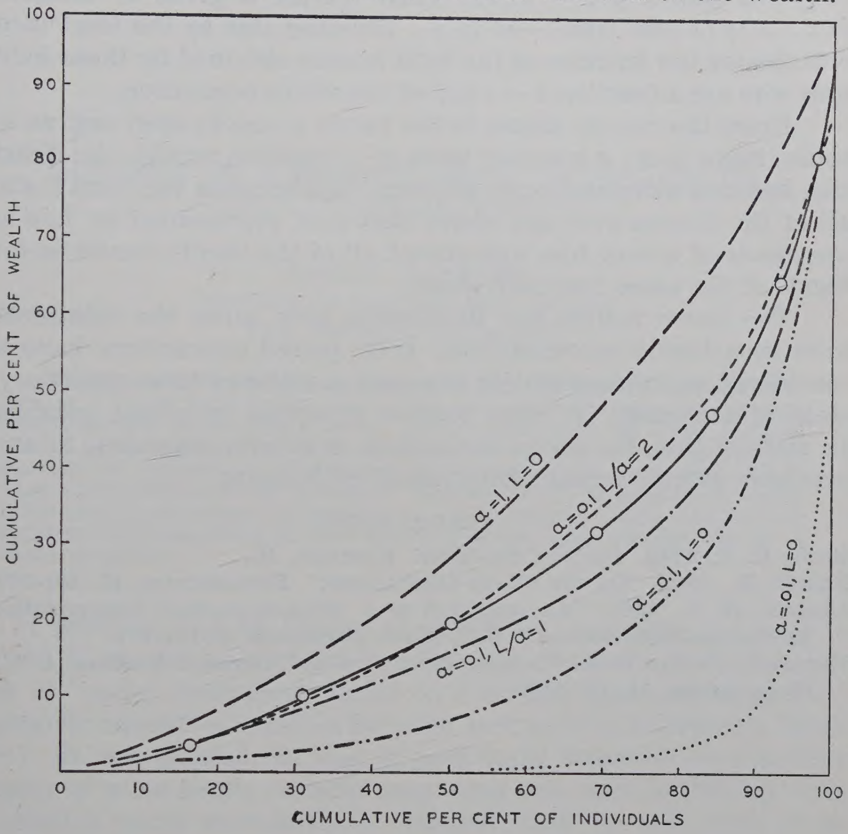

FIGURE 1

To illustrate the results some numerical examples are given in graphic form in Figure 1. Since we shall consider only the steady state and since the income and wealth are in this case linear with each other, we shall refer to income only. The cases for which $B = 0$ and $\alpha = 0.01$, $L = 0$; $\alpha = 0.1$, $L = 0$, $L/a = 1$, $L/a = 2$; $\alpha = 1$, $L = 0$ are shown. Since only relative values are used in the figure the values of $(P - L)\tau/\theta\gamma$ were not calculated. To illustrate the type of distribution which actually occurs, the 1935–36 distribution of incomes (families and single) in the United States is given in the figure also.

The calculations were made by taking $W(0, \infty)$ as the unit of wealth, then determining $W(x, \infty)$ from equation (12) together with the condition (13). From these values, $I(x, \infty)$ is obtained by adding L [equation (17)]. The fraction of individuals which have values of x less than x is $1 - z(x)$. Their income is given by integrating $I(x', \infty)p(x')dx'$ from $-\infty$ to x. Dividing this by the total income, one obtains the fraction of the total income obtained by these individuals who are a fraction $1 - z(x)$ of the whole population.

From the results shown in the figure it can be seen that as α becomes large (e.g., a becomes large or γ becomes small), the distribution becomes more and more uniform. If α becomes very small, almost all of the income over and above that part represented by L/a is in the hands of a very few, and almost all of the wealth would be in the hands of the same few individuals.

The above results are illustrative only, since the relationships have been highly oversimplified. Only paired interactions have been considered and the population has been considered to be stationary instead of changing. No other random processes have been considered. In spite of this, the above mechanism is able to represent, to an appreciable extent, actual distributions of incomes.

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OUTLINE OF A PROBABILISTIC APPROACH TO ANIMAL SOCIOLOGY: III

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The probabilities of the emergence of the two kinds of social structure in a 3-bird flock (chain and cycle) are deduced under the assumption of certain biases acting on the social dynamics of the flock. In particular a bias against the reversal of peck order and a bias against encounters of individuals of disparate social rank are considered. Likewise a distribution of an "inherent" fighting ability is considered which influences the outcomes of encounters.. A functional relation is derived between the importance of this ability and the initial probability of a chain structure.

In previous papers (Rapoport, 1949a,b), hereafter referred to as I and II, we have studied the probability distributions for various types of "social structures" based on a certain asymmetric, but not necessarily transitive, relation between each pair of individuals (peck right). It was pointed out that if peck right depended on a definite quantity of some single variable associated with each individual, then the relation would necessarily be transitive and the only types of social structure would be simple chains of the form

$$A > B > \cdots Z . \tag{1}$$

Structures involving cycles ($A > B > C > A$) have, however, been observed, and this led us to formulate a number of probabilistic approaches to the theory of the origin of structures, where the outcomes of encounters and thus the emerging of structures is, in part at least, determined by chance events.

In I and II we have examined the distributions of structures emerging from the most "unbiased" kinds of encounters where the probability of victory is always 1/2 for each individual in any encounter. Certainly this is a highly idealized situation. Actually, as has been shown (Collias, 1943) many factors tend to favor victory. Some of these are intrinsic (characteristic of the individual over long periods of time, for example, size of comb); some are accidental (present over short periods, for example, moulting); some are "historical" (connected with the history of the individual, for example, social rank).

In our approach we are interested not so much in the outcomes of encounters between single individuals as in the kinds of social structures that are likely to arise in small flocks. An experimental situation for this approach would be the study of a very large number of small flocks with the view of determining the frequencies with which various types of structure occur initially and in the long run. In the present paper, therefore, we shall inquire how various types of bias influence the probability distribution of those structures.

Bias against Reversal of Peck Right.

It was assumed in II that from time to time encounters take place between individuals in a flock and that as a result of such encounters the peck right may be preserved or reversed with equal probability. Under these assumptions, the ultimate, steady state distribution of structures was computed. We shall now introduce a bias *against* the reversal of peck right, that is, victory is more probable for the dominant individual in any pair. Let us see how this bias affects the ultimate distribution.

The fundamental quantities used in the computation of ultimate distributions are the "social mutation" probabilities, a_{ij}, that is, the probabilities that as a result of some single encounter, structure S_i shall mutate to structure S_j. Evidently

$$a_{ij} = \sum_{k=1}^{l(i,j)} e_k^{(ij)} r_k^{(ij)}, \tag{2}$$

where $e_k^{(ij)}$ are the probabilities of those encounters which may affect the mutation S_{ij}, and r_k are the corresponding probabilities of peck right reversal in those encounters.

In a completely unbiased situation, all the $e_k^{(ij)}$ are equal to $[\frac{1}{2}N(N-1)]^{-1}$, since all encounters are equally probable; furthermore all the r_k are equal to $\frac{1}{2}$. However $l(i, j)$ varies with the pair (i,j). Thus, for the case of three individuals $l(1,2) = 1$, since only one encounter can affect the mutation S_{12}; but $l(2,1) = 3$ since every encounter in a cyclic flock can affect S_{21}. Therefore in that case $a_{12} = 1/6$; $a_{21} = 1/2$.

In introducing an anti-reversal bias, we are now modifying the weighting factors r_k. We shall consider first the case of three individuals.

Let $\delta_0 \leq \frac{1}{2}$ and $\delta_2 \leq \frac{1}{2}$ be the corresponding biases against the reversal of peck right between two individuals whose social rank differs by 0 and 2 respectively. The case where $\delta_0 = \delta_2 = \frac{1}{2}$ reduces to the case studied in I, where the structure is completely determined after the initial encounters. Therefore we shall suppose that $\delta_0\delta_2 < 1/4$, i.e., not both quantities are equal to $1/2$. The corresponding bias for individuals differing in social rank by 1 is irrelevant, because encounters between these individuals do not affect mutations. Then

$$\begin{aligned} a_{12} &= 1/3(1/2 - \delta_2) = 1/6 - \delta_2/3; \\ a_{11} &= 5/6 + \delta_2/3; \\ a_{21} &= 1/2 - \delta_0 . \end{aligned} \tag{3}$$

We have seen in II that the ultimate probability for structure S_1 (simple chain) is given by

$$S_1 = \frac{a_{21}}{1 - a_{11} + a_{21}}. \tag{4}$$

Therefore

$$\begin{aligned} S_1 &= \frac{1/2 - \delta_0}{1/6 - \delta_2/3 + 1/2 - \delta_0} = \frac{1/2 - \delta_0}{2/3 - \delta_0 - \delta_2/3} \\ &= \frac{3}{2} \cdot \frac{1 - 2\,\delta_0}{2 - 3\,\delta_0 - \delta_2}. \end{aligned} \tag{5}$$

This quantity will be greater than $3/4$ (the unbiased ultimate probability of S_1) provided

$$\begin{aligned} &\frac{1 - 2\,\delta_0}{2 - 3\,\delta_0 - \delta_2} > 1/2; \\ &2 - 4\,\delta_0 > 2 - 3\,\delta_0 - \delta_2; \\ &\delta_2 > \delta_0 . \end{aligned} \tag{6}$$

The result is quite obvious intuitively, since the condition $\delta_2 > \delta_0$ means that the social ranks of the individuals with 2 and 0 dominant peck rights tend to be preserved more than the social ranks of individuals with 1 dominant peck right. But individuals with 2 and 0 peck right are found only in the simple chain structure. Hence the simple chain structure tends to be preserved. Incidentally, the condition that the ultimate structure shall be *certainly* a chain is

$$\begin{aligned} S_1 &= \frac{3}{2}\,\frac{1-2\,\delta_0}{2-3\,\delta_0-\delta_2} = 1; \\ &\frac{1-2\,\delta_0}{2-3\,\delta_0-\delta_2} = 2/3; \\ &3-6\,\delta_0 = 4-6\,\delta_0-2\,\delta_2; \\ &\delta_2 = 1/2\,. \end{aligned} \tag{7}$$

In other words, given the bias here considered a necessary and sufficient condition that the ultimate structure of the three individual society shall be certainly a chain is that no reversal of peck right shall ever take place between two individuals whose social rank differs by 2.

It is easy to see that the analogous condition for the ultimate certainty of the cycle is $\delta_0 = 1/2$. The case $\delta_0 = \delta_2 = 1/2$ is indeterminate. But, as has been pointed out, this reduces to the case treated in I.

Bias against Encounters between Individuals of Disparate Rank.

The only logical bias in the case of three individuals is against the encounter between the individuals with 2 and 0 dominant peck right respectively. Then, if ε denotes this bias, ($\varepsilon < 1/3$) we have

$$\begin{aligned} a_{12} &= (1/3-\varepsilon)1/2 = 1/6-\varepsilon/2; \\ a_{21} &= 1/2; \\ S_1 &= \frac{1/2}{1/6-\delta/2+1/2} = 3\cdot\frac{1}{1-3\,\varepsilon+3} = \frac{3}{4-3\,\varepsilon}. \end{aligned} \tag{8}$$

Again we see that ultimate probability for S_1 approaches unity as ε approaches $1/3$, i.e., as encounter between individuals of disparate rank becomes impossible.

If both kinds of biases are operating, the following formula for S_1 is easily derived by completely analogous methods

$$S_1 = 3\,\frac{1-\delta_0}{4-6\,\delta_0-3\,\varepsilon-2\,\delta_2+6\,\varepsilon\,\delta_2}.$$

This simple case suggests that the biases operating in favor of the ultimate establishment of chain hierarchies may have to do with the lowering of the probability of encounter or the probability of peck right reversal between individuals of disparate rank. We have seen in I that every structure except the simple chain must contain individuals of equal social rank, that is, possessing the same number of dominant peck rights. Now each encounter between such individuals resulting in a reversal of peck right increases the rank of the winner and decreases the rank of the loser. If encounters and reversals are confined to individuals of equal social rank, then conceivably the society will gravitate toward a structure in which there are no individuals of equal social rank, and that is a chain structure. It would be artificial, of course, to impose such a condition on an actual flock, since it is highly improbable that a bird is able to compare its social rank with that of every other bird. It may be aware of its particular *peck right relations* with every other bird in the flock, but can be hardly supposed to be able to count the number of dominant peck rights enjoyed by itself and by its potential rival. However it is conceivable that the attitude of one bird toward another may roughly depend on the social rank of the other quite apart from the particular peck right relation between the two. Thus if a bird sees another bird pecked *often,* that is, by many others, it may fight it, even though the particular peck right relation between them may be in favor of the other bird. On the other hand the leading position may tend to be preserved, because no bird ever sees the leader pecked at all. All these tendencies favor the ultimate establishment of a chain hierarchy as shown mathematically in the simple case of three individuals.

Distribution of an Inherent Quantity.

Suppose now that each individual is endowed with a certain quantity of some property x which is important in fighting. It is by no means certain that the individual with the greater x will always be victorious in an encounter but his chances are in general the better the greater the excess of his x over that of his opponent. We may make the probability of victory of individual X_1 over that of X_2 a function of $(x_1 - x_2)$ where x_1 and x_2 are the respective fighting qualities of X_1 and X_2. This treatment is quite analogous to H. D. Landahl's treatment of the probability of guessing the stronger of two stimuli in a discrimination test. (Landahl, 1938, 1939, 1940.)

Let now $F(x)$ be the distribution of the quantity x in the entire population which is to be divided into flocks. To fix ideas we take our flocks to be triples. The range of x can be any convenient one, and we shall take it as $0 \leqq x \leqq 1$ so that $F(x)dx$ is the fraction of the total population with x lying in the interval $(x, x + dx)$ and

$$\int_0^1 F(x)\,dx = 1 .$$

Then the probability that three individuals X, Y and Z characterized by x, y and z respectively have been selected to form some flock will be $F(x)F(y)F(z)\,dxdydz$. Suppose $V(x-y)$ is the probability that X wins an encounter with Y. We seek the expression that a triple becomes a chain as a result of the three *initial* encounters. A chain can be formed as a result of the following mutually exclusive events

$$\begin{aligned}&(X>Y)\cdot(Z>Y) \quad \text{or} \quad (Y>Z)\cdot(X>Z)\\ &\text{or } (Y>X)\cdot(Z>X).\end{aligned} \tag{9}$$

Here $X > Y$ means X wins over Y. Note that the necessary and sufficient condition for a chain in a triple is that one individual is pecked by the other two, where the peck order of the other two is immaterial. Hence the probability of a chain in the initial distribution is given by

$$\begin{aligned}&\int_0^1\int_0^1\int_0^1 V(x-y)V(z-y)F(x)F(y)F(z)\,dxdydz\\ &+\int_0^1\int_0^1\int_0^1 V(x-z)V(y-z)F(x)F(y)F(z)\,dxdydz\\ &+\int_0^1\int_0^1\int_0^1 V(y-x)V(z-x)F(x)F(y)F(z)\,dxdydz\,.\end{aligned} \tag{10}$$

To solve an actual problem, we must, of course, make assumptions on the forms of F and V. We shall make the simplest possible assumption on F, namely that any value of x is equally likely in a sample. $F(x)$ is then a "rectangular" distribution: $F(x) = 1$, $0 \leqq x \leqq 1$. As for $V(\xi)$, where ξ is $(x-y)$, $(z-y)$, or whatever the case may be, we would like it to be of sigmoid form such as the usual case with error functions. For large positive values of ξ, $V(\xi)$ should be unity or nearly unity; for large negative values $V(\xi)$ should approach zero, while for small absolute values of ξ, $V(\xi)$ should be nearly $1/2$, since those are the cases where victory is a matter of chance.

One such function is $V(\xi) = \int_{-\infty}^{\xi} e^{-t^2}dt$, which is expressible in terms of the incomplete gamma function. However, this function does not lend itself to integration in closed form. We wish, however, to solve some cases in closed form in order to illustrate the method. We shall therefore devise some rough approximations.

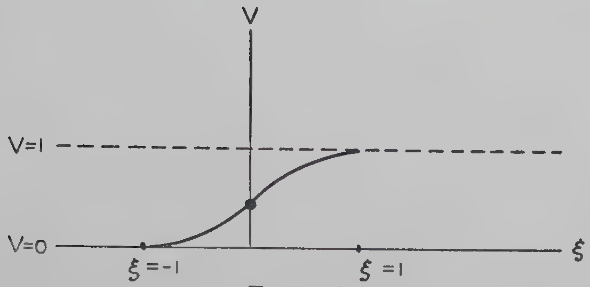

FIGURE 1

Polynomial Approximations.

Our sigmoid function has the general characteristics of Figure 1. The range of ξ is $-1 \leqq \xi \leqq 1$, since the ranges of x, y, and z are all $(0, 1)$. Let us find a polynomial approximating such a curve within the range of ξ. We assume that the victory of the individuals with the highest x over that of the individual of the lowest x is a certainty. Therefore if $f(\xi)$ is the desired polynomial, we must have

$$\begin{gathered} f(-1)=0; \quad f(0)=1/2; \quad f(1)=1; \\ f'(-1)=f'(1)=0; \quad f''(0)=0. \end{gathered} \tag{11}$$

To satisfy these six conditions, a polynomial of at most sixth degree is sufficient. However, the symmetry of the curve with respect to the point $(0, 1/2)$ helps to determine it more precisely. By the method of undetermined coefficients one can easily derive the polynomial

$$f(\xi)=1/2+m\,\xi-(2m-5/4)\,\xi^3+(m-3/4)\,\xi^5, \tag{12}$$

where m is an arbitrary parameter. This polynomial satisfies the conditions (11). If we further demand that $f(\xi)$ have no turning points between -1 and 1 and no inflexions in that range except at zero, this puts some restrictions on m. It is sufficient to demand that no inflexions except at $\xi=0$ occur between -1 and 1 since the existence of turning points for this polynomial in that range implies the existence of inflexion points. Taking the second derivative, we have

$$f''(\xi)=-(12m-15/2)\,\xi+(20m-15)\,\xi^3. \tag{13}$$

One of the roots of (13) is zero and this represents the inflexion at $\xi=0$. The other roots are given by

$$\xi=\pm\sqrt{\frac{24m-15}{40m-30}}, \tag{14}$$

and we wish these to be greater than unity in absolute value or else imaginary. In the first case, the range of m can be seen to be $3/4 \leqq m \leqq 15/6$; in the second it is $5/8 \leqq m \leqq 5/4$. Since both ranges of m preserve the shape of the curve in Figure 1, we may allow the total range $5/8 \leqq m \leqq 15/16$.

Evidently m is the slope of the curve at $\xi = 0$. The larger the m, the more abrupt is the change in the probability of victory of X over Y as the quantity $(x - y)$ changes sign. Hence the quantity m is a sort of measure of the importance of the inherent fighting ability in determining victory. If m is large, the results of outcomes are more determined; if it is small the results are more random. It would be interesting to establish the functional relation between m and the probability distribution of the two structures of triples after the initial encounters. However, the polynomial approximation allows us only a comparatively narrow range for m. For this reason, we shall compute the probability distribution only for the simplest case, $m = 3/4$ and take up the discussion of the functional relation between m and the probability distribution in connection with another approximation.

If $m = 3/4$, $f(\xi) = 1/2 + m\xi - (2m - 5/4)\xi^3$. We wish to compute the quantity

$$\int_0^1 \int_0^1 \int_0^1 f(x-y) f(z-y)\, dx dy dz . \tag{15}$$

We perform the integration with respect to z first.

$$\begin{aligned} \int_0^1 f(x-y) f(z-y)\, dz &= f(x-y) \int_0^1 f(z-y)\, dz \\ &= f(x-y)\,[13/16 - 6/2 + 3y^2/8 + y^3/4] . \end{aligned} \tag{16}$$

Next we perform the integration with respect to x. We note that the bracket in (16) is independent of x, while $f(x - y)$ is exactly of the same form as $f(z - y)$. Therefore the result of the two integrations is

$$13/16 - y/2 + 3y^2/8 + y^3/4 . \tag{17}$$

Integrating (17) with respect to y, we obtain after elementary but laborious computations the value .285, which is 1/3 of the probability of a chain. Hence the probability of a chain is in this case

$$S_1 = .855 , \tag{18}$$

which is significantly larger than the random probability 3/4.

Absolute Exponential Approximation.

We shall now let our sigmoid curve be represented by the following function:

$$V(\xi) = \tfrac{1}{2}e^{m\xi} \qquad \text{for} \quad \xi \leqq 0;$$
$$V(\xi) = 1 - \tfrac{1}{2}e^{-m\xi} \qquad \text{for} \quad \xi \geqq 0. \tag{19}$$

This function is continuous and has a continuous first derivative but a discontinuous second derivative at $\xi = 0$. It is seen to be the integral of the absolute exponential function $e^{-m|\xi|}$, which has been used by H. D. Landahl (1938) as an approximation to a normal distribution. The function $V(\xi)$ is a good approximation to the error function. It does not have the values 0 and 1 at $\xi = -1$ and 1 respectively, but this simply means that we are abandoning our hypothesis that victory of the strongest over the weakest individual in the population is a certainty. This is equivalent to choosing a smaller sample. The range of m is here quite unrestricted ($0 \leqq m < \infty$). The extreme cases are instructive. For $m = 0$, victory is arbitrary, and the case reduces to that treated in I. For $m = \infty$, victory of the stronger individual is certain, and the probability of the chain must be unity. Thus for $m = 0$, we must have $S_1 = 3/4$; for $m = \infty$, $S_1 = 1$. These values will serve as a check on our computations.

We are interested in the quantity

$$\int_0^1 \int_0^1 \int_0^1 V(x-y)\,V(z-y)\,dxdydz\,, \tag{20}$$

which gives 1/3 of the probability of a chain. To compute the integral (20), we divide the region of integration into four nonoverlapping regions in which the functions V and limits of integration are as follows:

Region	$V(x-y)$	$V(z-y)$	Limits of x and z
1. $(x-y) < 0$; $(z-y) < 0$	$\frac{1}{2}e^{m(x-y)}$	$\frac{1}{2}e^{m(z-y)}$	$0 \leqq x \leqq y$; $0 \leqq z \leqq y$
2. $(x-y) < 0$; $(z-y) > 0$	$\frac{1}{2}e^{m(x-y)}$	$1 - \frac{1}{2}e^{-m(z-y)}$	$0 \leqq x \leqq y$; $y \leqq z \leqq 1$
3. $(x-y) > 0$; $(z-y) < 0$	$1 - \frac{1}{2}e^{-m(x-y)}$	$\frac{1}{2}e^{m(z-y)}$	$y \leqq x \leqq 1$; $0 \leqq z \leqq y$
4. $(x-y) > 0$; $(z-y) > 0$	$1 - \frac{1}{2}e^{-m(x-y)}$	$1 - \frac{1}{2}e^{-m(z-y)}$	$y \leqq x \leqq 1$; $y \leqq z \leqq 1$

The range of y is $0 \leqq y \leqq 1$ for all cases. Thus we must evaluate the following sum of integrals

$$\begin{aligned}&\int_0^1\int_0^y\int_0^y \tfrac{1}{4}e^{mx-2my+mz}\,dxdzdy\\ &+\int_0^1\int_y^1\int_0^y \tfrac{1}{2}e^{m(x-y)}[1-\tfrac{1}{2}e^{-m(z-y)}]\,dxdzdy\\ &+\int_0^1\int_0^y\int_y^1 [1-\tfrac{1}{2}e^{-m(x-y)}]\,\tfrac{1}{2}e^{m(z-y)}\,dxdzdy\\ &+\int_0^1\int_y^1\int_y^1 [1-\tfrac{1}{2}e^{-m(x-y)}][1-\tfrac{1}{2}e^{-m(z-y)}]\,dxdzdy\,.\end{aligned} \tag{21}$$

The integrations are laborious but straightforward and yield in the last result

$$1/3+\frac{9-4m-2e^{-m}(4+3m)-e^{-2m}}{4m^3}. \tag{22}$$

Multiplying expression (22) by 3, we obtain the probability of a chain as a function of m, namely,

$$S_1=1+\frac{27-12m-6e^{-m}(4+3m)-3e^{-2m}}{4m^3}. \tag{23}$$

We note that $\lim\limits_{m\to\infty} S_1=1$, as should be the case. For $m=0$, the expression is indeterminate, since both the numerator and the denominator vanish. However it can be easily evaluated by L'Hôpital's rule after three differentiations. Thus upon differentiating the numerator and denominator of the fraction in (23) once we obtain

$$\frac{-12+6e^{-m}(4+3m)-18e^{-m}+6e^{-2m}}{12m^2}, \tag{24}$$

which is still indeterminate for $m=0$.

On second differentiation, we get

$$\frac{-6e^{-m}(4+3m)+18e^{-m}+18e^{-m}-12e^{-2m}}{24m} \tag{25}$$

still indeterminate.

But finally on third differentiation we obtain

$$\frac{6e^{-m}(4+3m)-54e^{-m}+24e^{-2m}}{24}, \tag{26}$$

whose limit as m approaches zero is $-1/4$. Thus $\lim\limits_{m\to 0} S_1=3/4$, as desired.

The above method illustrates how a functional relation between the importance of inherent characteristics and the distribution of social structures can be found. The actual experimental problem is, of course, far less determinate. In general what will be observed is the distribution of structure types, from which it is desired to determine the bias parameters. We have seen how several bias parameters may be responsible for the deviation of the actual structure distribution from the random distribution. Obviously a single experimental situation will not enable us to say which bias factors are actually at work. However if independent observations are made in societies of, say, 3, 4 and 5 individuals, the problem becomes much more definite, since different assumptions on the biases for the case of three individuals may lead to widely different conclusions as to what will happen in flocks of 4 and 5 individuals.

The 4-bird flock already shows marked differences from the 3-bird flock. In the latter the probability of a chain is a priori high (3/4). In the former the a priori probability of a chain is quite low (1/8). Thus if a predominance of chains is observed in 4-bird flocks, one must conclude the operation of biases. On the basis of what is assumed about the biases operating in a 3-bird flock, certain predictions may be made about the dynamics of the 4-bird and the 5-bird flocks. Eventually a theory may be developed which would describe the actual evolution *in time* of the structure distribution acted upon by various sorts of bias (so far we have considered only initial and final distributions). It is hoped that these studies may help in the development of a mathematical sociology.

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ON THE SINGLE EVENT HYPOTHESIS IN RADIOGENETICS

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It is shown that the assumption of a cumulative action of many independent random events as the primary cause of induction of a mutation fits the experimental data at least equally as well as the single event hypothesis. The theory is illustrated on the existing data of X-ray induced lethals in the X-chromosome of *Drosophila*. Possible shortcomings of the single event theory in connection with these experimental data and alternative ways of its modification are indicated.

The idea that a gene mutation induced by an ionizing radiation is due to a single primary event has its basis mainly, if not exclusively, in the quantitative relationship between the amount of energy used, D, and the detected frequency, P, of the mutation. In fact, if the experimental values of P are plotted against D, the result can be frequently well fitted by the curve

$$P(D) = 1 - \exp(-kD), \tag{1}$$

k being a constant. In general the range of kD is so small that the graph of $P(D)$ appears as a straight line (cf. e.g. Timoféeff-Ressovsky, 1937, pp. 67, 123; Sturtevant and Beadle, 1940, p. 210; Catcheside, 1948, pp. 327–330). Considering the energy D as a very large number of ionizing particles or ionizations and interpreting equation (1) probabilistically (cf. e.g. Uspensky, 1937, pp. 135–137; Cramér, 1946, p. 203), we see that one ionizing particle or one ionization is sufficient to cause the observed mutation; if the energy D is measured as the number of ionizations per unit of volume, k in formula (1) is the size of the volume within which the ionization must occur to produce the mutation.

U. Fano and M. Demerec (1944) warned against an unqualified acceptance of the concept of a single all-or-none event as a primary cause of a radiation induced mutation; the latter may appear as initiated by such an event only because the observable genetical effect is of this kind by its nature: either there is a mutation or there is not, although mutations of the continuously varying or of the quantitative character may perhaps offer an exception to this latter viewpoint. In a recent paper (Opatowski, 1950) the author has pointed out that other interpretations of experimental results equally plausible, but incompatible with the single event theory, can lead to a relationship between P and D, which within the range covered by the existing experimental data does not differ from formula (1) by more than the experimental errors. The purpose of this note is to obtain such an interpretation through a different mathematical procedure and to apply it to different experimental results.

Let us assume that the primary cause of the observed mutation is a cumulative action of a very large number of mutually independent events, e.g. ionizations. The central limit theorem of the theory of probability translated into non-mathematical terms tells us that if a phenomenon is a consequence of a very large number of mutually independent random causes, then the quantitative characteristic of this phenomenon, measured e.g. by the probability of occurrence of a certain event, follows the normal law of probability (Castelnuovo, 1925, vol. I, p. 160; vol. II, p. 187; Uspensky, 1937, chap. XIV; Cramér 1946, pp. 213–220). In more precise terms we can state this theorem and apply it here in the following manner (cf. Opatowski, 1950): Let us consider a gene in the irradiated sample. Let the first event (e.g. the first ionization) be induced in that gene by a dose $\Delta_1 D$, the second event by a dose $\Delta_2 D$, the third by $\Delta_3 D$, etc. Since each of these events either consists of or is due to an ionization and since the occurrence of an ionization at a particular point in the sample is a random event, each of the $\Delta_i D$'s is a random variable insofar as the induction of the ith event in the gene is concerned. It is justified to assume that all these random variables $\Delta_i D$ $(i = 1, 2, 3, \cdots n)$ are mutually independent and that they have the same probability distribution; there are no reasons for making the opposite suppositions. Consequently the distribution of

$$\sum_{i=1}^{i=n} \Delta_i D$$

tends to be normal as n tends to infinity (central limit theorem, see e.g. Cramér, 1946, p. 215). If we apply this theorem here by assuming that the mentioned events are caused by absorptions of some amounts of the administered energy, then the probability of inducing a mutation in a sample through an increase of the amount of energy absorbed from D to $D + dD$ is:

$$dP = A \exp[-h^2 (D - M)^2]\, dD, \tag{2}$$

where A, h and M are constant. Each value of D gives a certain frequency of mutation P. The latter is not zero when $D = 0$, because of spontaneous mutations. If we indicate with S the dose that would have to be given to the sample to induce in it the genetical effects existing in it in a natural manner and related to the particular mutation considered, if the sample were completely free from those effects, then the theoretically significant range of D extends from $-S$ up to the maximum value of the dose actually used in the experiment. Whereas the frequency of spontaneous mutations is a genetical measure of the degree of transformation which the population undergoes, the quantity S gives an idea about the magnitude of the energies which may be involved in this process. At the present stage of our knowledge about the mechanism of spontaneous mutations this or any other interpretation of S must be very inconcrete: it is expressed in terms of ionizing energy, which—at least in organisms of not very long life span—is known to be insignificant for the process of spontaneous mutation. However S is needed for the purpose of a mathematical analysis which is here carried out.

If we assume that an infinite amount of energy $D = \infty$ would induce mutation in the entire sample, i.e., if we put $P = 1$ for $D = \infty$, then we obtain from equation (2) as the probability $P(D)$ of inducing mutation during the administration of a dose D

$$P(D) = \int_{-S}^{D} \exp\left[-h^2(x-M)^2\right] dx \Big/ \int_{-S}^{\infty} \exp\left[-h^2(x-M)^2\right] dx\,,$$

or

$$1-P(D) = [1-H(hD-hM)]/K\,, \qquad (3)$$

where $K = 1 + H(hS + hM)$ and $H(x)$ is the error integral (WPA, 1941), and

$$H(x) = (2/\sqrt{\pi}) \int_{0}^{x} \exp(-x^2)\,dx\,. \qquad (4)$$

The above formulae give the probability of spontaneous mutation for $D = 0$. Except for a displacement of the origin of the system of coordinates and for different units of length of the two axes, the function $P(D)$ given by equation (3) and the integral $H(D)$ are identical.

Considering now the original question as to the correctness of the hypotheses upon which equation (1) is based, we may ask to what extent do the functions $P(D)$ as defined by equations (1) and (3) differ from each other in the range in which $P(D)$ is experimentally known? The question is not easy to answer in this general form, because three parameters h, M and S appear in equation (3). However we have noticed already that, except for a linear transforma-

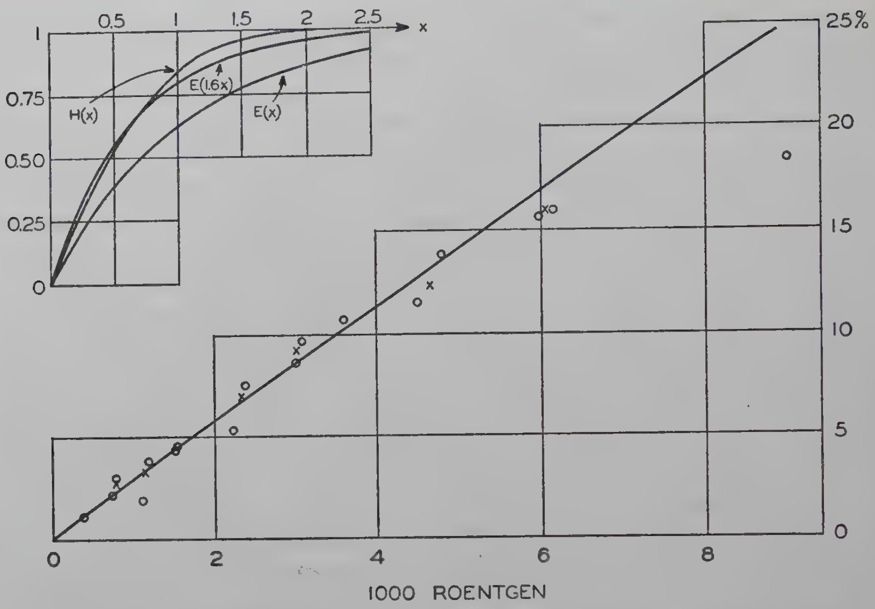

FIGURE 1. The upper diagram to the left represents the error integral $H(x)$ and the curves

$$E(gx) = 1 - \exp(-gx)$$

for $g = 1$ and $g = 1.6$. Among all the $E(g)$'s the curve $E(1.6x)$ is about the best approximation to $H(x)$ (see the Addendum to this paper).

The lower diagram to the right gives the frequency of lethal mutations induced by X-rays in the X-chromosome of *Drosophila*. The dots represent the data of I. Schechtman (1930), W. P. Efroimson (1931), C. P. Oliver (1932) and N. W. Timoféeff-Ressovsky (1934). The crosses are weighted averages calculated by K. G. Zimmer (1934). Crosses overlapping with dots have been omitted. The curve is calculated from equation (3) with $S = 42$, $M = 6600$ and $h = 0.00003$.

tion of coordinates, the function $P(D)$ of equation (3) is identical with $H(hD)$. For instance, in the very particular case in which $M = S = 0$, we have $P(D) = H(hD)$. A comparison of the graphs of the function $H(x)$ and of the function $P(x)$ as expressed by equation (1) for $k = 1$, shows that they do not differ by very much (see Fig. 1). The difference between $H(hx)$ and the function $P(x)$ of equation (1) can be further reduced by choosing an appropriate value of h for each value of k. An analysis in an Addendum to this note shows that over the whole positive range of D the approximation

$$H(hD) \approx 1 - \exp(-kD), \qquad \text{with } k/h = 1.6 \tag{5}$$

is about the best. For sufficiently small values of D the relation $H(hD) \approx 2hD/\sqrt{\pi}$ holds, consequently in this range $k/h \approx 2/\sqrt{\pi} \approx 1.13$. It is seen from the figure that the difference between the two sides of equation (5) is not large even over the whole infinite range of D if suitable parameters k and h are used. This difference can be made still smaller over partial ranges of D. This fact suggests on mathematical grounds that drawing conclusions as to the type of the primary process of a radiation induced mutation from experimental data on mutation frequency and dose may be misleading, since opposite types of processes, that of a single random event and of many independent random events may imply the same quantitative relationship, within experimental errors.

To test this possibility in a more concrete manner the figure shows a well known set of sex-linked lethals induced in *Drosophila* by X-rays, fitted by equation (3) with $S = 42$, $M = 6600$ and $h = 0.00003$, where roentgen is taken as the unit of the dose. The fit is about as good as those known in the literature based on equation (1) [see e.g. Timoféeff-Ressovsky, 1937, p. 67; Sturtevant and Beadle, 1940, p. 211]. All of these fits including the present one are very close to a linear one, within the range of D up to about 6000 roentgen, and all show about the same magnitude of deviation from the experimental data at higher doses. The recently published data of W. P. Spencer and C. Stern (1948) on the lethal mutations in *Drosophila,* which are not included in the figure, can be fitted quite well with the same values of S and M, and a value of $h = 0.000025$ (Opatowski, 1950). From a statistical viewpoint the distribution (2) as it is used in the present paper is a truncated normal distribution. If it were not truncated at $D = -S$ but used up to $D = -\infty$, the constant h would be inversely proportional to the standard deviation. This may explain why the experiments considered in this paper give a higher h than the fit of W. P. Spencer's and C. Stern's results alone, since the latter involve a smaller number of experimental data and consequently may show a larger standard deviation.

It should be noted that there is no function (1) which would fit all the data of Figure 1 on the lethal mutation in the X-chromosome of *Drosophila*; the lower curve of Figure 1 is not only a fit by equation (3) but is also about the best fit based on equation (1). Consequently if the mutation frequency of 18.3% at 9000 roentgen found by I. Schechtman and W. P. Efroimson is correct, the single event theory would not hold for the mutation considered. Two facts have to be kept in mind in this connection:

(a) The dose of 9000 roentgen is very high, since 10,000 roentgen give a complete sterilization according to W. P. Efroimson (1931). Above the range of about 6200 roentgen there are no other experimental data on the mutation considered, except that just mentioned of Schechtman and Efroimson. The latter fit well to a smooth curve together with the remaining data (Fig. 1), including those of

C. P. Oliver at 6160 roentgen and N. W. Timoféeff-Ressovsky at 6000 roentgen (cf. K. G. Zimmer, 1934). The other data of Efroimson and Schechtman, for instance, at 4500 roentgen with 11.5% mutation frequency agree very well with the figure of Timoféeff-Ressovsky of 13.77% at 4800 roentgen (cf. Zimmer, 1934). Consequently there are no indications that the results of Efroimson and Schechtman might be incorrect.

(b) The complete set of data as they are available today pertinent to the lethal mutation considered is in disagreement with the theory that mutation is induced by a single event of one type. However these data do not conflict with the assumption that there are *two different events,* each capable of inducing a lethal independently of the other. This assumption would give a relation of the type

$$P(D) = 1 - pe^{-kD} - (1-p)e^{-hD}, \quad \text{with } 0 < p < 1, \tag{6}$$

instead of equation (1), and would maintain the essential characteristics of the single event theory, except that it would imply that two different mutational processes are actually taking place, although no differences between the end products of these mutations are detected. It is very likely that equation (6) can be well fitted to the data of Figure 1; however, such a fit must involve essentially different values of k and h, because otherwise equation (6) would be practically identical with equation (1). Since k and h are the volumes within which the events discussed must take place to be effective, the question arises whether the order of magnitude of k and h, as obtained from such a fit, agrees with the presently accepted figures of this volume. We leave this question open for the present. Equation (6) which has never been considered for *Drosophila,* has been recently suggested for bacteria, on different grounds though than those here indicated (Cavalli and Visconti, 1948, 1949).

The present paper presents some doubts, on a theoretical basis, about the validity of the single event theory in radiogenetics and indicates the type of mathematical work that still could be done to investigate these doubts further. Doubts on the same subject have been expressed also on more direct experimental grounds (Caspari and Stern, 1948), although they do not seem to be entirely confirmed by the more recent investigations of D. E. Uphoff and C. Stern (1949).

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ADDENDUM

Putting $hD = x$, $k/h = g$, $E(gx) = 1 - \exp(-gx)$, $R(g, x)$

$= H(x) - E(g, x)$, the problem of obtaining the best approximation of the type (5) may be stated as the problem of finding a value of g such that the maximum value that $|R(g, x)|$ takes as x varies be as small as possible. The solution of this problem is dependent on the range of x considered. The range 0 to $+\infty$ is here discussed. In order to carry out this discussion the intersection points $x = x_0$ of the curves $H(x)$ and $E(gx)$ must be examined first (cf. the figure). These points are solutions of the equation:

$$g = -x_0^{-1} \ln [1 - H(x_0)].$$

The quantity $g(x_0)$ is an increasing function of x_0 for $x_0 > 0$. Its graph is very close to a straight line in the range of x_0 from 0 to 2.8. It passes through the point $x_0 = 0$, $g = 2/\sqrt{\pi}$; consequently the curves $H(x)$ and $E(gx)$ do not intersect each other in the positive range of x if $g < 2/\sqrt{\pi} \approx 1.13$.

We can discuss the problem of the best approximation $E(g, x) \approx H(x)$ by splitting the range of g into two intervals $0 < g < 2/\sqrt{\pi}$ and $g \geqslant 2/\sqrt{\pi}$. (Negative g's do not have any meaning in the genetical problem considered.) Consider first $0 < g < 2/\sqrt{\pi}$. In this interval $R(g, x)$ is positive, and for any constant g the maximum value of $R(g, x)$ is attained when x is the positive root x_m of the equation

$$x_m^2 - gx_m + \ln(g\sqrt{\pi}/2) = 0. \tag{7}$$

Since here $0 < g < 2/\sqrt{\pi}$, this equation has one and only one positive root. The value of $R(x_m, g)$ plotted against g appears as a decreasing function of g with its smallest value ≈ 0.165 at the end of this range, i.e., for $g = 2/\sqrt{\pi}$ (the corresponding value of x_m is also $2/\sqrt{\pi}$).

The approximation just obtained, through $g = 2/\sqrt{\pi}$, can be still improved if $g \geqslant 2/\sqrt{\pi}$ is considered. In fact, in this range equation (7) has two positive roots x_m which correspond each to a maximum value of $|R(x, g)|$ as x varies and g is fixed. As g is increased (beyond $2/\sqrt{\pi}$) one of these maximum values of $|R(x, g)|$ decreases, starting from ≈ 0.165 at $g = 2/\sqrt{\pi}$; the other maximum value, however, increases, starting from 0 at the same value of g. Consequently under the condition $g \geqslant 2/\sqrt{\pi}$, the best approximation $H(x) \approx E(g, x)$ is obtained when these two maxima are equal; this occurs about at $g \approx 1.6$ and gives $|R(x_m, g)| \approx 0.05$ (for $x_m = 1.34$ and 0.26). Since 0.05 is smaller than 0.165 we conclude that $g \approx 1.6$ gives the best approximation of the error integral $H(x)$ by the function $E(g, x) = 1 - \exp(-gx)$ over the whole positive range of x.

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A PROBLEM IN RADIOBIOLOGY: DIFFUSION AND RECOMBINATION OF IONS

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A perturbation treatment is given for the cylindrically symmetrical distribution of ions or their products resulting from the passage of a single ionizing particle, and taking into account ion diffusion and recombination. The results apply to cases in which diffusion is more important than recombination.

We are concerned with the ion distribution resulting from the passage of a single ionizing particle or ray through a homogeneous medium. It is assumed that the ionizing particle travels in a straight line, and that in the absence of an external field the ion distribution is cylindrically symmetrical. The ions or their products* resulting from the radiation diffuse and simultaneously recombine at a rate proportional to the product of their concentrations.

The partial differential equation describing this process is nonlinear so that an explicit solution is hardly to be expected. An approximate treatment, that is still used, was first given by G. Jaffé (1913); for another approximation see A. N. Gerritsen (1948). In this paper we treat the problem by a perturbation method, and calculate the first few perturbation terms, which makes a more accurate determination of the distribution possible in cases in which diffusion is more important than recombination. The applications to radiobiology and the delimitation of the situations in which these results can be applied will not be discussed here, but will be considered in later papers by I. Opatowski.

Assuming that the diffusion coefficient, D, is the same for both positive and negative ions or their products, then the partial differential equation for ion concentration is

$$\frac{\partial n}{\partial t} = D \nabla_r^2 n - \alpha n^2, \qquad 0 \leq r < \infty ; \tag{1}$$

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*H atoms and OH radicals in the case of water.

where n = concentration of either positive or negative ions,

t = time,

$\nabla_r^2 = \frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r}$, Laplacian,

r = distance from the path of the ionizing particle,

α = recombination coefficient.

For the initial condition, we take, as is usually assumed (Jaffé, 1913; Kara-Michailova and Lea, 1940),

$$n(r,0) = \frac{N_0}{\pi b^2} e^{-\frac{r^2}{b^2}}. \tag{2}$$

Here, N_0 is the number of ionizations produced by the ionizing particle per unit length of path, and b is a measure of the initial radius of the ion column.

In the following we use the method of sources and sinks or the method of Green's function (Carslaw and Jaeger, 1947). This method allows us to give an interpretation to the initial condition (2). The distribution in (2) is seen to be the same as that resulting from from an instantaneous line source of strength N_0, acting at time t,

$$t = -\frac{b^2}{4D},$$

in the case of diffusion without recombination. That is, (2) is equivalent to assuming that the ionizing particle instantaneously produces N_0 ions per unit of path length, and that these ions diffuse outward without recombination for a time, $b^2/4D$, before recombination begins. Of course, the actual process is more complicated, involving collisions off the path of the ionizing particle.

In order to simplify the expressions which follow it is convenient to introduce the following dimensionless variables:

$$\nu = \frac{\pi b^2}{N_0} n, \tag{3}$$

$$\rho = r/b, \tag{4}$$

$$\tau = \frac{D}{b^2} t, \tag{5}$$

$$\beta = \frac{\alpha N_0}{\pi D}. \tag{6}$$

Then equations (1) and (2) become

$$\frac{\partial \nu}{\partial \tau} = \nabla_\rho^2 \nu - \beta \nu^2, \qquad 0 \leq \rho < \infty; \tag{7}$$

$$\nu(\rho, 0) = e^{-\rho^2}. \tag{8}$$

To solve this system by the perturbation method we assume that ν may be expressed as a power series in β,

$$\nu = \sum_{k=0}^{\infty} \beta^k \nu_k(\rho, \tau). \tag{9}$$

Substituting in (7) and (8) and equating equal powers of β, we find

$$\frac{\partial \nu_0}{\partial \tau} = \nabla_\rho^2 \nu_0, \qquad \rho \geqslant 0; \tag{10}$$

$$\nu_0(\rho, 0) = e^{-\rho^2}; \tag{11}$$

and for $k > 0$,

$$\frac{\partial \nu_k}{\partial \tau} = \nabla_\rho^2 \nu_k - \sum_{j=0}^{k-1} \nu_j \nu_{k-1-j}, \qquad \rho \geqslant 0; \tag{12}$$

$$\nu_k(\rho, 0) = 0. \tag{13}$$

Now it is known that the distribution due to an instantaneous cylindrical surface source at time, $\tau = 0$, which liberates one ion per unit area of cylinder and has radius, σ, is (Carslaw and Jaeger, 1947)

$$G(\rho, \sigma; \tau) = \frac{\sigma}{2\tau} \exp\left[-\frac{\rho^2 + \sigma^2}{4\tau}\right] I_0\left(\frac{\rho\sigma}{2\tau}\right), \tag{14}$$

where I_0 is the Bessel function of zero order and imaginary argument. This can be used to write the solutions of systems (10) and (11) or (12) and (13) in the form of integrals. The solution of

$$\frac{\partial \nu}{\partial \tau} = \nabla_\rho^2 \nu + \psi(\rho, \tau), \qquad \rho \geqslant 0; \tag{15}$$

$$\nu(\rho, 0) = \phi(\rho); \tag{16}$$

is

$$\begin{aligned} \nu(\rho, \tau) &= \int_0^\infty \phi(\sigma) G(\rho, \sigma; \tau)\, d\sigma \\ &+ \int_0^\tau d\lambda \int_0^\infty \psi(\sigma, \lambda) G(\rho, \sigma; \tau - \lambda)\, d\sigma. \end{aligned} \tag{17}$$

Using this formula the value of ν_0 is

$$\nu_0(\rho\,,\tau) = \int_0^\infty e^{-\sigma^2}\, G(\rho\,,\sigma\,;\tau)\; d\,\sigma\,. \tag{18}$$

To evaluate the integral in (18) we need the formula

$$\int_0^\infty e^{-c^2x^2}\, I_0(ax)\, x\; dx = \frac{1}{2c^2}\, e^{\frac{a^2}{4c^2}} \quad , \tag{19}$$

which is readily established by using the power series for I_0. Then we obtain

$$\nu_0(\rho\,,\tau) = \frac{e^{-\frac{\rho^2}{4\tau+1}}}{4\tau+1} \quad . \tag{20}$$

This, of course, gives the distribution for $\alpha = 0$, no recombination. It could have been anticipated from the interpretation of the initial condition as the distribution due to an instantaneous source, since (20) is the distribution due to an instantaneous line source at time, $\tau = -\frac{1}{4}$, for diffusion without recombination. It is the first approximation given by G. Jaffé (1913).

From (17) we can now calculate ν_1 as

$$\nu_1(\rho\,,\tau) = \mathcal{G}[-\nu_0{}^2(\rho\,,\tau)] =$$

$$-\int_0^\tau d\,\lambda \int_0^\infty \frac{e^{-\frac{2\sigma^2}{4\lambda+1}}}{(4\lambda+1)^2}\; G(\rho\,,\sigma\,;\tau-\lambda)\,d\lambda\,, \tag{21}$$

where we use $\mathcal{G}$ to denote the second integral operator in (17), that is,

$$\mathcal{G}\,[\psi(\rho\,,\tau)] = \int_0^\tau d\,\lambda \int_0^\infty \psi(\sigma\,,\lambda)\,G(\rho\,,\sigma\,;\tau-\lambda)\,d\,\lambda\,. \tag{22}$$

It is convenient to introduce a new time variable

$$\zeta = 4\tau + 1 = (4Dt + b^2)/b^2, \tag{23}$$

and correspondingly

$$\mu = 4\lambda + 1; \tag{24}$$

then using (19), we obtain after some manipulation

$$\nu_1 = -\frac{1}{4}\int_1^\zeta \exp\left[-\frac{2\rho^2}{2\zeta-\mu}\right]\frac{d\,\mu}{\mu(2\zeta-\mu)}\,, \tag{25}$$

which can be reduced to

$$\begin{aligned}\nu_1 &= -\frac{e^{-\rho^2/\zeta}}{8\zeta} \int_{\rho^2/\zeta(2\zeta-1)}^{\rho^2/\zeta} e^{-x}\,\frac{dx}{x} \\ &= \frac{e^{-\rho^2/\zeta}}{8\zeta}\left[Ei(-\rho^2/\zeta) - Ei(-\rho^2/\zeta(2\zeta-1))\right],\end{aligned} \tag{26}$$

where

$$-Ei(-x) = \int_x^{\infty} e^{-t}\,\frac{dt}{t} \tag{27}$$

is the exponential integral which has been extensively tabulated (Jahnke and Emde, 1943; Mathematical Tables Project, 1940). It may be readily verified directly that (26) satisfies the equation for ν_1.

We have also calculated the next term, ν_2, which has a rather complicated expression. Starting with

$$\nu_2 = \mathcal{G}[-2\,\nu_0\,\nu_1], \tag{28}$$

and using the formula

$$\begin{aligned}&\int_0^{\infty}\left[\int_{b_1x^2}^{b_2x^2} e^{-y}\,\frac{dy}{y}\right] e^{-c^2x^2}\, I_0(ax)\,x\,dx \\ &= \frac{e^{\frac{a^2}{4c^2}}}{2c^2} \int_{\frac{a^2}{4c^2}\frac{b_1}{c^2+b_1}}^{\frac{a^2}{4c^2}\frac{b_2}{c^2+b_2}} e^{-z}\,\frac{dz}{z},\end{aligned} \tag{29}$$

which is readily established by a change of variable and interchange of order of integration, we obtain after some manipulation

$$\nu_2 = \frac{e^{-\rho^2/\zeta}}{8\zeta} \int_{\rho^2/\zeta(2\zeta-1)}^{\rho^2/\zeta} \left[\int_L^U e^{-y}\,\frac{dy}{y}\right] e^{-x}\,\frac{dx}{x}, \tag{30}$$

with

$$L = \left[\frac{8\,\rho^2}{\left(\frac{\rho^2}{\zeta} + x\right)^2} - \frac{1}{x}\right]^{-1};$$

$$U = \left[\frac{3}{x} - \frac{4}{\frac{\rho^2}{\zeta} + x} \right]^{-1} ;$$

One of the quantities of principal interest is the total number of ions per unit path length,

$$N(t) = \int_0^\infty 2\pi r n \, d r = 2N_0 \int_0^\infty \nu \rho \, d\rho . \tag{31}$$

Let the fractional number of ions be

$$M(t) = N(t)/N_0 . \tag{32}$$

The contribution to $M(t)$ from ν_0 and ν_1 could be calculated directly, but the use of the following formula is simpler and also makes the calculation of the contribution of ν_2 possible. Referring to the system (15) and (16), we obtain by integrating over the region bounded by $\rho = 0$, $\rho = \infty$, $\tau = 0$, $\tau = \tau$,

$$\int_0^\infty \nu \rho \, d\rho = \int_0^\infty \phi(\rho) \rho \, d\rho + \int_0^\tau d\tau \int_0^\infty \psi(\rho, \tau) \rho \, d\rho , \tag{33}$$

which is a form of Green's theorem for this system; and physically simply states that the total number of ions is equal to the initial number plus the additional number generated by the sources. Then we obtain

$$M_0 = 2 \int_0^\infty \nu_0 \rho \, d\rho = 1 ; \tag{34}$$

$$\begin{aligned} M_1(\tau) = 2 \int_0^\infty \nu_1 \rho \, d\rho = -2 \int_0^\tau d\lambda \int_0^\infty \frac{e^{-\frac{2\rho^2}{4\lambda+1}}}{(4\lambda+1)^2} \rho \, d\rho = \\ -\tfrac{1}{8} \log(1 + 4\tau) ; \end{aligned} \tag{35}$$

$$M_2(\tau) = \tfrac{1}{8} \int_1^{1+4\tau} \frac{d\mu}{\mu^2} \int_0^\infty e^{-\frac{2\rho^2}{\mu}} \left[\int_{\rho^2/\mu(2\mu-1)}^{\rho^2/\mu} e^{-x} \frac{dx}{x} \right] \rho \, d\rho .$$

Integrating by parts [or using limiting case of (29), $a \to 0$], we find

$$M_2(\tau) = \frac{1}{32}\int_1^{1+4\tau} \log\left(\frac{4\mu-1}{3}\right)\frac{d\mu}{\mu}$$

$$= \frac{1}{32}\int_1^{1+4\tau}\left[\log\frac{4}{3}\mu + \log\left(1-\frac{1}{4\mu}\right)\right]\frac{du}{\mu} = \frac{1}{64}\left\{\left[\log\frac{4}{3}(1+4\tau)\right]^2 \right. \tag{36}$$

$$\left. - \left(\log\frac{4}{3}\right)^2\right\} + \frac{1}{32}\int_{\frac{3+16\tau}{4+16\tau}}^{\frac{3}{4}} \log u \frac{du}{u-1}.$$

The last integral is a tabulated function (Powell, 1943).

For large values of τ, $M_2(\tau) \rightarrow [\frac{1}{8}\log(1+4\tau)]^2$, so that $M \cong M_0 + \beta M_1 + \beta^2 M_2$ approaches the first three terms of the expansion of the approximation arrived at by Jaffé (1913),

$$N/N_0 = \left[1 + \frac{\alpha N_0}{8\pi D}\log\left(1+\frac{4D}{b^2}t\right)\right]^{-1}. \tag{37}$$

D. E. Lea (1947) considers the case in which the two types of ion products, H atoms and OH radicals, have different diffusion coefficients, D_1 and D_2, and the columns have correspondingly different initial radii, b_1 and b_2. For this case it is not difficult to calculate the first two terms of the perturbation calculation of N, by the same method as was just used. The result is

$$N/N_0 = 1 - \frac{\alpha N_0}{4\pi(D_1+D_2)}\log\left[1 + 4\left(\frac{D_1+D_2}{b_1^2+b_2^2}\right)t\right], \tag{38}$$

which is the same as the first two terms in the expansion of expression given by Lea.

Our previous simplified interpretation of $\frac{b^2}{4D}$ as the diffusion time before the start of recombination can be applied to the numerical values given by D. E. Lea (1947). These give 8×10^{-9} sec. for H atoms, and 0.5×10^{-9} sec. for OH radicals.

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NOTE ON THE GLYCOLYTIC COEFFICIENT

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The glycolytic coefficient of a cell is expressed as a function of the external concentrations of glucose, lactic acid and oxygen. It is shown that this function has a smallest value when the external concentration of glucose is zero and a certain inequality between the external concentrations of lactic acid and of oxygen is satisfied.

The glycolytic coefficient β of a cell is an important constant, occurring in the theory of cell division and cancer research as developed by N. Rashevsky (1948). This theory raises a number of problems which might be attacked by minimizing the glycolytic coefficient β. The latter will be the purpose of the present work. From the theory of cell respiration of N. Rashevsky (1936) and H. D. Landahl (1937, 1939) the glycolytic coefficient β can be expressed as a function of the external concentrations c_{01}, c_{02} and c_{03} of glucose, lactic acid and oxygen respectively.

Denoting

$$c_{03} = x, \quad c_{02} = y, \quad c_{01} = z;$$
$$a\Lambda_1 + 1 = p;$$
$$a\Lambda_2 = r;$$
$$pnf\Lambda_2 = s;$$
$$pf\Lambda_3 = t;$$
$$af\Lambda_2\Lambda_3 = u;$$
$$2\Lambda_3 f^2 p^2 \Lambda_2 n = v;$$
$$2\Lambda_3 f^2 p \Lambda_2{}^2 n\, a = w;$$

[in which a, f, Λ_i $(i = 1, 2, 3)$ have the same meaning as in the first above-mentioned work], we find as the result of elementary calculations:

$$\beta = \frac{p}{3(py + rz)} \cdot \left[\frac{2rz}{sx - ty - uz - p + \sqrt{(sx + ty + uz + p)^2 - 2vxy - 2wxz}} - y \right]. \tag{1}$$

Denoting further for abbreviation:

$$sx + ty + uz + p = A(x, y, z); \tag{2}$$

$$\sqrt{(sx + ty + uz + p)^2 - 2vxy - 2wxz} = B(x, y, z); \tag{3}$$

$$\begin{aligned} &sx - ty - uz - p \\ &\quad + \sqrt{(sx + ty + uz + p)^2 - 2vxy - 2wxz} = C(x, y, z); \end{aligned} \tag{4}$$

we get

$$\beta = \frac{p}{3(py + rz)}\left(\frac{2rz}{C} - y\right). \tag{5}$$

Simplification of

$$\frac{\partial \beta}{\partial x} = 0; \quad \frac{\partial \beta}{\partial y} = 0; \quad \frac{\partial \beta}{\partial z} = 0; \tag{6}$$

leads to respectively:

$$z\left(s + \frac{sA - vy - wz}{B}\right) = 0; \tag{7}$$

$$-\frac{p}{py + rz}\left(\frac{2rz}{C} - y\right) - \frac{2rz\left(-t + \frac{tA - vx}{B}\right)}{C^2} - 1 = 0; \tag{8}$$

$$-\frac{p}{py + rz}\left(\frac{2rz}{C} - y\right) + \frac{2rC - 2rz\left(-u + \frac{uA - wx}{B}\right)}{C^2} = 0. \tag{9}$$

Unfortunately, it is impossible to satisfy these three equations (7), (8) and (9) simultaneously. However, it is easy to see that $z = 0$ satisfies the first and second equation, while the rather wide condition $sx - ty \geqslant 0$ or, what amounts to the same thing,

$$c_{03} \geqslant \frac{\Lambda_3}{n\Lambda_2}\, c_{02},$$

assures that the left-hand member of equation (9) is positive. Therefore, in this case

$$\frac{\partial \beta}{\partial x} = 0; \quad \frac{\partial \beta}{\partial y} = 0; \quad \frac{\partial \beta}{\partial z} > 0,$$

so that β has a smallest value when z is as small as possible. The latter then has the value $z = 0$, because the physical meaning of z allows it only to have values which are at least 0.

Concluding, we see that when $z = 0$ and $c_{03} \geqslant \dfrac{\Lambda_3}{n\Lambda_2} c_{02}$, β has a smallest value, being $-\frac{1}{3}$.

The meaning of the negative sign of the glycolytic coefficient has been discussed by N. Rashevsky (1948, p. 74).

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A NOTE ON LANDAHL'S THEORY OF PSYCHOPHYSICAL DISCRIMINATION

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In his theory of psychophysical discrimination H. D. Landahl assumes that because of the symmetry of the neural circuit considered the fluctuation of the difference of excitations at the two parallel connections is the same as if the fluctuations occurred only at either one of the connections. It is shown that if the excitation at both connections fluctuates independently according to a simple exponential probability function, the difference of excitation fluctuates according to a different probability function.

In his theory of psychophysical discrimination H. D. Landahl (1937) [cf. also Rashevsky, 1948] assumes random fluctuation of excitation in the two parallel cross-inhibited pathways. Because of the symmetry of the whole structure a positive fluctuation on one side is equivalent to a negative fluctuation on the other side. Therefore Landahl considered first fluctuations at only one of the two parallel connections.

In a subsequent paper (Landahl, 1940) it was shown that if the fluctuations are distributed according to the Gaussian law, then the results are the same, regardless of whether one set of fluctuations occurs at one connection or two independent fluctuations occur in both parallel chains.

Inasmuch, however, as a distribution different from the normal has been introduced by H. D. Landahl, and found more convenient for deriving closed expressions, it is interesting to investigate the case of two independent fluctuations for such a distribution.

The purpose of this note is to show that in this case the restriction to one fluctuation is not always justified, although it does not necessarily invalidate Landahl's results. In fact what is essential in Landahl's theory is to assume that the difference,

$$\Delta = \varepsilon_1 - \varepsilon_2 \, , \tag{1}$$

fluctuates according to some distribution function $p(x)$, such that

$$\int_{-\infty}^{+\infty} p(x)\,dx\,, \tag{2}$$

and where $p(x)\,dx$ denotes the probability of a fluctuation between x and $x+dx$. This does not mean, however, as we shall see, that either ε_1 or ε_2 individually fluctuates according to the *same* function $p(x)$.

Let $\varDelta > 0$ for the sake of definiteness and consider the probability P_w of the (wrong) reaction R_2 when both ε_1 and ε_2 fluctuate independently according to some function $p(x)$.

Suppose that at a given moment ε_1 has a fluctuation ϕ, while ε_2 has a fluctuation ϕ', so that instead of $\varepsilon_1 - \varepsilon_2$ we now have $(\varepsilon_1 + \phi) - (\varepsilon_2 + \phi')$. Considering for simplicity the case of two categories, that is, $h = 0$ (Landahl, 1937; Rashevsky, 1948), we find that for R_2 to occur we must have $(\varepsilon_1 + \phi) - (\varepsilon_2 + \phi') < 0$, or

$$\phi' > \varDelta + \phi\,. \tag{3}$$

Hence for a given ϕ, any value of ϕ' which satisfies (3) will result in the reaction R_2.

But, for a fixed ϕ, the probability of inequality (3) is given by

$$\int_{\Delta+\phi}^{\infty} p(x)\,dx = F(\varDelta + \phi). \tag{4}$$

Since the probability of ϕ being between ϕ and $\phi + d\phi$ is $p(\phi)\,d\phi$, the probability of R_2 for a given ϕ is equal to

$$F(\varDelta + \phi)\,p(\phi)\,d\phi\,. \tag{5}$$

Since ϕ may have any value from $-\infty$ to $+\infty$,

$$P_w = \int_{-\infty}^{+\infty} F(\varDelta + \phi)\,p(\phi)\,d\phi = \int_{-\infty}^{+\infty} p(\phi)\,d\phi \int_{\Delta+\phi}^{\infty} p(x)\,dx\,. \tag{6}$$

Let us evaluate P_w under the assumption made by Landahl that

$$p(x) = \frac{k}{2}\,e^{-k|x|}. \tag{7}$$

Then we have

$$\text{for } x > 0 \qquad p(x) + p_+(x) = \frac{k}{2}\,e^{-kx}\,; \tag{8}$$

$$\text{for } x < 0 \qquad p(x) = p_-(x) = \frac{k}{2}\,e^{kx}. \tag{9}$$

For $\varDelta + \phi > 0$, or for $\phi > -\varDelta$, we find from (4):

$$F(x+\phi)=F_+(\Delta+\phi)=\frac{k}{2}\int_{\Delta+\phi}^{\infty} e^{-kx}dx=\tfrac{1}{2}\,e^{-k(\Delta+\phi)}. \tag{10}$$

For $\Delta+\phi<0$ or $\phi<-\Delta$ we find

$$\begin{aligned}F(\Delta+\phi)=F(\Delta+\phi)&=\frac{k}{2}\int_{\Delta+\phi}^{0} e^{kx}dx+\frac{k}{2}\int_{0}^{\infty} e^{-kx}dx\\&=1-\tfrac{1}{2}\,e^{k(\Delta+\phi)}.\end{aligned} \tag{11}$$

Remembering (8), (9), (10) and (11) we see that (6) now becomes

$$\begin{aligned}P_w=&\int_{-\infty}^{-\Delta} E_-(\Delta+\phi)p_-(\phi)\,d\phi+\int_{-\Delta}^{0} F_+(\Delta+\phi)p_-(\phi)\,d\phi\\&+\int_{0}^{\infty} F_+(\Delta+\phi)p_+(\phi)\,d\phi\,.\end{aligned} \tag{12}$$

Introducing (8), (9), (10) and (11) into (12) we find after rearrangements

$$P_w=\left(\frac{1}{2}+\frac{k\Delta}{4}\right)e^{-k\Delta}. \tag{13}$$

The quantity P_w decreases monotonically with Δ since

$$\frac{dP_w}{d\Delta}=-\frac{k}{4}(1+\Delta)\,e^{-k\Delta}<0. \tag{14}$$

Expression (13) differs, however, from that derived by Landahl, which is

$$P_w=\tfrac{1}{2}\,e^{-k\Delta}\,. \tag{15}$$

Thus we see that if Δ *as a whole* fluctuates according to the law given by (7), the probability P_w is less than if ε_1 and ε_2 fluctuate independently according to (7).

After reading this manuscript Professor H. D. Landahl has shown by a simple graphical construction that equations (13) and (15) can represent a given empirical curve equally well with a maximum difference of approximately 2%.

The author is indebted to Dr. Landahl for reading the manuscript and for the above contribution.

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ON THE REMOVAL OF AIR-BORNE DROPLETS BY THE HUMAN RESPIRATORY TRACT: I. THE LUNG*

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Calculations as to the fate of air-borne particles in the respiratory tract are given in a paper by W. Findeisen (1935). It is the purpose of the present paper to extend and modify these calculations. The results obtained for total retention in the lungs are found to be in general agreement with published data (cf. Landahl and Herrmann, 1948). The calculated results also give information on the amounts deposited in various regions as well as the amounts retained in different fractions of expired air.

Since the geometry of the respiratory passages is very complex, it is at best only possible to represent the important features and then assign approximate values to the average dimensions from observations. Since these values are very approximate it would seem necessary only to carry out calculations of the effect of the factors involved in an approximate manner. Furthermore, since several factors are acting to different degrees in various parts of the respiratory tract, the net result does not generally depend too much upon the effect of one factor of removal in any one region. For this reason we shall derive approximate relations for the three principal factors involved in the removal of particles by the respiratory tract.

Schematic Representation of the Respiratory Tract. In order to make an estimate for the probability of removal of any particle from the air stream, it is necessary to set up a model of the respiratory tract. In so doing, we follow the model of W. Findeisen (1935) fairly closely. The respiratory tract is represented by a tree in which regions of the same order are taken to be equivalent. In most cases the regions closely approximate cylindrical tubes. The "mouth" and "pharynx" are added, and two orders of alveolar ducts are used instead of one in order to reduce the very large branching factor. A few values are slightly changed to conform to measurements by various other investigators. But the principal changes are made to satisfy the requirement that the volumes calculated for the alveolar ducts and sacs be sufficiently large (cf. Willson, 1922; Loosli, 1949).

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TABLE I
SCHEMATIC REPRESENTATION OF RESPIRATORY TRACT

Region (α)	Number	Volume *cc*	Relative Volume V	Diameter $2R$ cm	Length cm	Cross Section Area	Velocity v	Passage Time τ'	Fraction Passing	τ^i
Mouth (1)	1	20	.04	2	7	3	100	.07	1.00	.07
Pharynx (2)	1	20	.04	3	3	7	45†	.07	.96	.06
Trachea (3)	1	25	.06	1.6	12	2	150	.08	.92	.074
Prim. Bronchi (4)	2	10	.02	1.0	6	.8	190	.032	.86	.027
Sec. B. (5)	12	4	.01	.4	3	.12	210	.014	.84	.012
Ter. Bron. (6)	100	5	.01	.2	1.5	.03	100	.015	.83	.012
Quart B. (7)	770	7	.015	.15	.5	.018	22	.023	.82	.02
Terminal (8) Bronchioles	6×10^4	50	.11	.06	.3	2.8×10^{-3}	1.8	.17	.81	.14
Resp. Bron. (9)	1.5×10^5	30	.06	.04	.15	1.2×10^{-3}	1.7	.09	.70	.06
Alveolar Ducts (10) I	3×10^6	100	.22	.03	.05	7×10^{-4}	.14	.36	.64	.25
Alveolar Ducts (11) II	4×10^7	600	(.42)	.025	.03	4.9×10^{-4}	.015	2.0	.42	.83
Alveolar Sacs (12)	10^8	(2000)	(0)	.033	.033		0			

†glottis velocity = 150

The numerical values of the geometrical measurements for the successive orders, α, are given in Table I. From these other values are calculated for a flow rate of 300 cc/sec., inspiration time of 1.5 sec., and 450 cc. tidal air. The last columns will be discussed subsequently.

Removal by Impaction Within Respiratory Passages. Because of its inertia, a particle suspended in an air stream will not be able to follow the stream as it bends around in its passage through the respiratory tracts; as a result, it may impact against the moist surface of a passage and be removed from the air stream. In this section we shall not consider impaction on cylindrical objects such as the nasal hairs. In the case of a tube, bent at 90 degrees, it is found (Landahl and Herrmann, 1949; cf. also May, 1945) that the fraction of the particles removed from the air stream is about one-half when the following relationship holds: $x \equiv \rho d^2 v/18\eta R = 1$, where ρ is the density and d is the diameter (cm) of the particles, v is the average velocity of the air stream, η is the viscosity of air (1.9×10^{-4} g cm^{-1} sec.$^{-1}$), and where R is the radius of the tube.

If we have a tube which bifurcates or branches, then the impaction in such a tube of order α, will be about fifty per cent when $\rho d^2 v_{\alpha-1} \sin\theta/18\eta R_\alpha = 1$. The quantity θ is the angle between the axes of the tubes of order $\alpha - 1$ and α. The quantity $v'_{\alpha-1} \sin\theta$ is the component of the velocity at right angles to the second tube. Actually, $v'_{\alpha-1}$ is not exactly the same as $v_{\alpha-1}$, the average velocity in a tube of order $\alpha - 1$, but the average velocity of that part going into a tube of order α. Unless the number of branches at one point is very large, the discrepancy is not serious, and $v'_{\alpha-1}$ is taken equal to $v_{\alpha-1}$ throughout. The average distance that the particle must pass perpendicular to the air stream is now R_α, the radius of the tube α, instead of R.

From the values given in Table I, it can be seen that the Reynolds' number (cf. Lamb, 1932) is in the general neighborhood of that which is required for turbulent flow. Thus we would expect the actual distribution of velocities to lie between a rectangular and a parabolic distribution. If all particles are moving at about the same speed, then the fraction which is removed by impacting against the outer wall at the bend of the tube would be roughly proportional to the ratio of the distance of slips through the air stream to the tube diameter. Therefore, in view of the result referred to in the preceding paragraph, the proportion would be roughly $\frac{1}{2}\rho d^2 v_{\alpha-1} \sin\theta/18R_\alpha\eta$ when this quantity is less than unity. On the other hand, if the velocity distribution is parabolic, the fraction which impacts would be less than the above linear approximation for very small x or for x much greater than unity, but the fraction would be greater than that given by the linear approximation for values of x about equal to unity. For example, a particle on the inner wall of the bend has a low velocity but must travel twice as far as a particle near the center of the tube, which travels with a higher velocity. These considerations suggest that if we choose the expression for the fraction removed by impaction to be of the form $x/(1+x)$, where $x = \rho d^2 v_{a-1} \sin \theta / 18 \eta R_a$, the result should be adequate, except perhaps for very small values of x. When $x=1$, the fraction is one-half. On the average, θ is about 30°. If $I_a{}^i$ denotes the fraction of material in section $\alpha - 1$ impacting in section α, due to inertia, we have

$$I_a{}^i = 150\, \rho\, d^2\, v_{a-1} / (R_a + 150 \rho\, d^2\, v_{a-1}) \qquad (1)$$

as the approximate equation determining the fraction impacted on inspiration. On expiration, the amount, $I_a{}^e$, would be the same except for the replacement of v_{a+1} by v_{a-1}. In the range of values actually used in the calculations, equation (1) gives substantially the same values as given by the rather complex equation derived by W. Findeisen.

Removal by Sedimentation. Due to the action of gravity, a particle settles downward through the air. In the absence of turbulence, particles of a given size very quickly attain a velocity such that the force of gravity is opposed by the force of friction. For particles that are not too small, the latter force can be calculated from Stoke's law (cf. Lamb, 1932), but if the particles become small enough to be comparable in diameter with the inter-molecular spaces of the air, the velocity is greater by a factor depending on the particle radius and the properties of the medium. If we write M_d for this factor, then (Findeisen, 1935)

$$M_d = 1 + 2 \times 10^{-5} (0.864 + 0.29\, e^{-6.25 \times 10^4 d}) / d\,,$$

or (Millikan, 1947)

$$M_d = 1 + 1.8 \times 10^{-5} / d\,, \qquad (2)$$

and the velocity of settling is

$$v_d = 2.9 \times 10^5\, \rho\, d^2\, M_d \text{ cm/sec.} \qquad (3)$$

vertically downward. Let the time that the particle remains in a region α be τ_a. In this time the particle would fall a distance $v_d\, \tau_a$. If a particular tube is inclined at an angle ψ with the horizontal, the vertical distance that a particle must fall before settling on the inner surface of the tube is increased by one over the cosine of the angle. The ratio of the distance of a fall, $v_d\, \tau_a$, to the maximum distance of the fall, $2R/\cos \psi$, is then $2.9 \times 10^5\, \rho\, d^2\, \tau_a\, M_d \cos \psi / 2R_a$, so that the fraction which settles out of the air stream will be roughly proportional to this quantity.

The average value of cos ψ for a randomly placed tube in three dimensions is $\pi/4$. We shall use this value with a few exceptions to be mentioned subsequently. In the absence of any turbulence each particle moves through the air a distance of one radius in the direction perpendicular to the tube when $2.3 \times 10^5 \rho\, d^2\, \tau_a\, M_d = R_a$. The area of intersection of two equal circles, each passing through the center of the other, is 39% of the area of either. If each particle moved down one radius, then all the particles not in the intersection would settle out, that is 61% is removed. Thus, if S is the fraction removed in section α due to sedimentation, $S = .61$ when $0.79\, v_d\, \tau_a = R_a$. If one makes the rough approximation that the relationship is linear, then a more careful analysis shows that S_a is slightly underestimated for small values of $v_d\, \tau_a/R_a$, but, of course, overestimated for large values of $v_d\, \tau_a/R_a$. The effect of any turbulence would be to increase S_a slightly for small values of S_a but to decrease S_a materially for larger values. Furthermore, the settling in quiet air, which occurs in the region of orders $\alpha - 1$, leaves the particle distribution in the region of order α altered, on the average, in a manner that slightly favors sedimentation for small S_a. If we set

$$S_a = 1 - e^{-1.8 \times 10^5 \rho\, d^2\, M_d\, \tau_a/R_a}, \tag{4}$$

then instead of 61% for $0.79\, v_d\, \tau_a/R_a$, we obtain 55%; while for small values of S_a we overestimate the settling in a single smooth section by a factor of about 1.25. In view of the above discussion, this expression for S_a should be a satisfactory approximation. If cos ψ is not taken equal to 0.79, then 1.8 should be replaced by 2.3 cos ψ. To calculate the sedimentation during inspiration, $S_a{}^i$, which in the calculations always equals the value for expiration, the quantity τ_a is set equal to $\tau_a{}^i$ (Table 1). For the sedimentation occurring when the breath is held, $S_a{}^h$, τ_a is set equal to τ^h, the time that the breath is held.

Removal by Brownian Movements. Small particles suspended in air are in continuous motion and after a short time will have moved appreciable distances. If D' is the diffusion coefficient for the particle in air, then the mean displacement after a time τ will be $\Lambda = \sqrt{2\, D'\, \tau}$ (Einstein, 1905). But, since $D' = kT^0/3\, \pi\, \eta\, d$, k being Boltzmann's constant per molecule, and T^0 the absolute temperature (Einstein, 1905), we have

$$\Lambda = \sqrt{2\, k\, T^0\, M_d/3\, \pi\, \eta\, d} = 6.85 \times 10^{-6} \sqrt{M_d\, \tau/d}\,. \tag{5}$$

in which the effective viscosity in the neighborhood of the particle is taken to be reduced by the same factor as in the case of settling. We may estimate the fraction of the particles removed by diffusion in a rough manner as follows: Suppose $\Lambda = 0.3R$. Consider a circle of radius R with another concentric circle of radius $0.7R$. Assume that the particles are moving only in three mutually perpendicular directions, one-sixth moving to the left, one-sixth to the right, etc. Consider the particles on the inner circle and on a horizontal axis. Of those moving to the right, one-half will travel $0.3R$ (since $\Lambda = 0.3R$), or $1/6 \times 1/2$ of the total. Of those moving to the left $(1/2)^{1.7/.3} = 0.02$ will be removed, or 0.003 of the total. Of those moving up or down $(1/2)^{.7/.3} = 0.20$ will be removed, or a total of $(1/6 + 1/6) \times 0.2 = 0.067$. Thus the total removed will be $0.083 + 0.003 + 0.067 = 0.153$. Since 0.7 is approximately equal to $2^{\frac{1}{2}}$, about one-half of all particles are initially interior to the circle of radius $0.7R$. For those inside the inner circle, the probability of removal will be less, whereas for those outside, the probability will be greater. Since the mean probability is not likely to be much different from the median calculated above, we ignore the discrepancy. For not too large values of Λ/R we can expect that the proportion of particles removed from the air stream due to Brownian motion is roughly proportional to Λ/R. However, for large values of Λ/R, the probability can approach unity only asymptotically. Since the free paths are distributed exponentially, an expression of the form $1-e^{-y}$, where y is proportional to Λ/R, is likely to be satisfactory. Hence, we may choose y such that for $P = 0.153$, $\Lambda = 0.3R$, and thus obtain for the fraction removed by diffusion, D_a, in section α:

$$D_a = 1 - e^{-4 \times 10^{-6}\sqrt{M_d\ \tau_a/d}/R_a}. \tag{6}$$

The values of D_a for inspiration or expiration, $D_a{}^i$, the fraction retained by diffusion during the pause, will be obtained from equation (6) with $\tau_a = \tau_a{}^i$, while $D_a{}^h$ is obtained by setting $\tau_a = \tau^h$. The values given by equation (6) are substantially the same as those given by calculations from the equations of W. Findeisen.

Wall Effect and Size Effect. Because of its size, a particle cannot have its center too close to the wall. This effect can be shown to play a very small role. Where the effect might be appreciable, other factors will have generally removed the particle. Similarly, for example, a particle need not impact, settle or diffuse the full distance required by the equations, since its radius should have been subtracted. Here again this is appreciable only when $d \underset{>}{\sim} 0.01$. But then either the obtained fraction is negligible, so that correcting it is unnecessary, or the correction becomes negligible when the fraction becomes appreciable. At most, these corrections increase the per cent retained by only a few per cent.

Calculations. We proceed to calculate the fractions of the air-borne particles which are retained in the various regions. Since we wish to compare results from deep breathing with shallow breathing, and in the former case the alveolar air exchange is a very large fraction of the tidal air whereas in the latter case the alveolar air exchange is negligible, we shall proceed with a somewhat more detailed calculation than that carried out by W. Findeisen. From equations (1), (4) and (6), together with the numerical values in Table I we can estimate the fraction of particles removed, due to any one factor, as the air passes from one region to the next. Then by successive calculations, which we shall now outline, the total amount removed in any one region can be obtained.

From the values given in Table I, the velocity in each region and the time of passage are calculated. Since part of the time is spent before reaching the region in question, the corrected times, τ_α^i, are obtained by multiplying τ_α' by the fraction passing, $1 - \sum_{\beta=1}^{\beta=\alpha-1} V_\beta$. These values are used throughout in the calculations. For the 4 sec. cycle, 300 cc./sec. the values are given in the last column of Table I.

For any region α, the fraction P_α^i of the material entering it, which is retained in the region, is the combined probability due to the three main factors: $P_\alpha^i = D_\alpha^i + I_\alpha^i + S_\alpha^i - D_\alpha^i I_\alpha^i - D_\alpha^i S_\alpha^i - I_\alpha^i S_\alpha^i + D_\alpha^i I_\alpha^i S_\alpha^i$ where each probability is a function of the transit time τ_α^i. Actually, at least one term is negligible and often all three are small, so that the calculation is not as involved as it appears. Let P_α^e be a similar compound probability for expiration. These probabilities differ only in that the expression for I in the latter is $I_\alpha(v_{\alpha+1}, R_\alpha)$ instead of $I_\alpha(v_{\alpha-1}, R_\alpha)$ as in equation (1), because of the reversed direction of flow. Let P_α^h be the probability of removal of the particle during the time that the breath is held constant, so that $I=0$ and the time τ_α in equations (4) and (6) is $T/8$, T being the time for a cycle. Let f_α be the fraction of the particles in a given volume of air which is still air-borne when it reaches region α. Then the fraction R_α^i of the material breathed which is retained in region α during inspiration is

$$R_\alpha^i = f_\alpha P_\alpha^i \sum_{\beta=\alpha}^{12} V_\beta, \qquad f_\alpha = (1-P_1^i) \cdots (1-P^i_{\alpha-1}), \tag{7}$$

that is, a fraction of the particles must have reached region α (f_α), must be removed (P_α^i) and only the fraction passing

$$\left(\sum_{\beta=\alpha}^{12} V_\beta = 1 - \sum_{\beta=1}^{\alpha-1} V_\beta \right)$$

is involved.

Similarly, for R_α^h, the amount retained during the period that the breath is held, we have

$$R_\alpha^h = f_\alpha(1 - P_\alpha^i) P_\alpha^h V_\alpha = f_{\alpha+1} P_\alpha^h V_\alpha , \qquad (8)$$

that is, the material must reach the region (f_α) but not be retained on entering $(1 - P_\alpha^i)$, and must be retained during the pause (P_α^h); the relative amount involved is V_α.

The relative concentration $C_{\beta,\beta}$ in region β after the pause is

$$C_{\beta,\beta} = f_\beta (1 - P_\beta^i)(1 - P_\beta^h). \qquad (9)$$

After the volume of air has passed back to region $\beta - 1$, the concentration becomes $f_\beta(1 - P_\beta^i) \times (1 - P_\beta^h)(1 - P^e_{\beta-1})$. If a volume of air reached a depth β, its concentration when returned to region $\gamma < \beta$ would be

$$C_{\gamma,\beta} = C_{\beta,\beta}(1 - P^e_{\beta-1})(1 - P^e_{\beta-2}) \cdots (1 - P_\gamma^e). \qquad (10)$$

The relative amount of the material which had reached a depth β but is retained in α on passing back out is the difference $C_{\alpha+1,\beta} - C_{\alpha,\beta}$. The total removed in α from all regions is then:

$$R_\alpha^e = \sum_{\beta=\alpha+1}^{12} V_\beta (C_{\alpha+1,\beta} - C_{\alpha,\beta}). \qquad (11)$$

Since particles on the average pass halfway into a region in which they stop, we shall consider removal upon entering the last region, but not upon leaving it. In order to obtain the total retained in region α we simply add $R_\alpha^i + R_\alpha^h + R_\alpha^e$, and the total retention is $R_T = \sum (R_\alpha^i + R_\alpha^h + R_\alpha^e)$. As a check we have the relation that the amount retained plus the amount coming out in the expired air must add up to unity. Thus it is useful to calculate separately the amount which is expired. The amount of air starting at region α (which had reached a depth α at the end of inspiration) is V_α and the fraction of particles remaining on expiration is $C_{1,\alpha}$. Thus the fraction in the expired air is given by

$$1-R_T=\sum_{\alpha=1}^{12} V_\alpha C_{1,\alpha}$$

$$=\sum_{\alpha=1}^{12} V_\alpha(1-P_1{}^i)(1-P_2{}^i)\cdots\cdot(1-P_\alpha{}^i)(1-P_\alpha{}^h) \qquad (12)$$

$$\cdot(1-P_\alpha{}^e)\cdots\cdot(1-P_1{}^e)\,.$$

In addition to being useful as a check on the calculations, this expression enables one to calculate the concentration in any part of the expired air, since one can obtain the sum over various intervals of α. The sum in any interval divided by the sum of the volumes for that interval gives the relative concentration.

Special Assumptions. In calculating the various probabilities some special assumptions have been made, a few of which are somewhat arbitrary. The velocity of the air entering the mouth at 18L/min. was taken to be 100 cm/sec., while the velocity of air entering the trachea (through the glottis) was in this case taken to be 150 cm/sec. Since the mouth is held nearly horizontally, a factor of 1.3 was introduced into the argument of the exponent, e.g. $\cos\psi = 1$. A similar factor was introduced for the pharynx. On the other hand, a factor of 1/3 is introduced for the trachea, which is nearly vertical in the experimental procedure. Since the alveolar ducts and sacs have very irregular surfaces which make settling and diffusion more effective, a factor of 1.3 was introduced for H, H' and I in the calculations of D and S. In addition, because of the essential spherical nature of the alveolar sacs, a factor of 1.5 was introduced, since there is a greater specific surface and no angle ψ involved. Since the alveolar ducts and sacs expand with inspiration, slightly larger values were used when the tidal air was larger. The three regions were assumed to increase by the same fractional volume so that the total volumes were in proportion to the residual volume plus one-half of the tidal air. The effect of mixing the air which is exchanged with the "dead" air is not taken into account in the calculations. This would tend to increase the calculated values of the retention.

The respiratory pattern chosen for the calculations is the following: Inspiration, at constant rate, 3/8 of a cycle; pause 1/8 cycle (τ^h, no inspiration or expiration); expiration 3/8 cycle; pause 1/8 cycle.

Results. In Table II, the calculations for one set of conditions are given to show the steps which must be carried out to obtain the values sought. Columns 2 and 3 are obtained from the data of Table

TABLE II

Calculations for 300 cc/Sec. 4 Sec. Cycle, 450cc Tidal Air

$\rho = 1$, $d = 20$ microns.

α	I_α^i	I_α^e	S_α^i	S_α^h	V_α	P_α^i	f_α	P_α^h	$\sum_{\beta=\alpha}^{12} V_\beta$	R_α^i	R_α^h	P_α^e	R_α^e	R_T	$C_{1,\alpha}$	$V_\alpha C_{1,\alpha}$
1	.06	.09	.07	.37	.04	.13	1.00	.37	1.00	.130	.013	.10	.002	.145	.55	.022
2	.04	.06	.04	.27	.04	.08	.87	.27	.96	.068	.009	.10	.005	.082	.53	.021
3	.10	.13	.02	.14	.06	.12	.80	.14	.92	.088	.007	.15	.005	.100	.49	.029
4	.15	.20	.04	.50	.02	.18	.70	.50	.86	.108	.006	.23	.001	.115	.20	.004
5	.36	.23	.04	.83	.01	.39	.58	.83	.84	.190	.003	.26	0	.193	.032	.000
6	.55		.08	.97	.01	.59	.35	.97	.83	.171	.001		0	.172	.002	0
7	.44		.18	1.0	.015	.54	.14	.99	.82	.062	.001		0	.063	.00	0
8	.31		.97	1.0	.11	.98	.07	1.0	.81	.055	.000		0	.055	.00	0
9	.05		.89	1.0	.06	.90	.001	1.0	.70	.001	.000		0	.001	.00	0
10	.07		1.0	1.0	.22	1.0	0	1.0	.64	.000	.000		0	.000	.00	0
11			1.0	1.0	.42	1.0	0	1.0	.42	.000	.000		0	.000	.00	0
12									.00	.000	.000		0	.000	.00	0
Total										.873	.040		.013	.926		.076

TABLE II (Continued)

	$C_{\alpha,\beta}$				
$\beta \diagdown \alpha$	1	2	3	4	5
1	.548	.526	.488	.199	.032
2		.584	.542	.221	.035
3			.602	.246	.039
4				.290	.046
5					.060

	$C_{\alpha+1,\beta} - C_{\alpha,\beta}$				
$\beta \diagdown \alpha$	1	2	3	4	5
1		.058	.054	.022	.003
2			.060	.025	.004
3				.044	.007
4					.017
5					

I and equation (1), columns 4 and 5 from Table I and equation (4). Column 7 is the compound probability obtained from columns 2 and 4, while column 9 is the same as column 5 since $I = 0$ during the pause and $D = 0$ for such a large particle size. Column 8 is obtained from column 7 by equation (7). Columns 11 and 12 are obtained from the preceding columns by the use of equations

TABLE III

RETENTION IN VARIOUS REGIONS OF THE RESPIRATORY TRACT

	300cc/sec., 4 sec. cycle 450cc tidal air					300cc/sec., 8 sec. cycle 900cc tidal air					300cc/sec., 12 sec. cycle 1350cc tidal air					1000cc/sec., 4 sec. cycle 1500cc tidal air				
	Diameter					Diameter					Diameter					Diameter				
α	20	6	2	.6	.2	20	6	2	.6	.2	20	6	2	.6	.2	20	6	2	0.6	0.2
1	15	0	0	0	0	14	1	0	0	0	14	1	0	0	0	18	1	0	0	0
2	8	0	0	0	0	8	1	0	0	0	8	1	0	0	0	10	1	0	0	0
3	10	1	0	0	0	11	1	0	0	0	11	1	0	0	0	19	3	0	0	0
4	12	2	0	0	0	13	2	0	0	0	13	1	0	0	0	20	5	0	0	0
5	19	4	0	0	0	17	4	1	0	0	18	5	1	0	0	21	12	3	0	0
6	17	9	0	0	0	20	9	1	0	0	21	10	1	0	0	9	20	4	1	0
7	6	7	1	0	0	8	7	1	0	0	8	7	1	0	1	1	10	2	0	0
8	6	19	4	2	2	6	24	6	2	2	6	24	6	1	2	1	9	2	0	0
9	0	11	4	2	2	0	10	4	2	2	0	12	4	2	2	0	3	1	2	2
10	0	25	16	5	6	0	27	19	7	9	0	27	20	8	8	0	13	10	4	5
11	0	5	28	10	9	0	5	48	21	18	0	5	49	24	23	0	17	41	16	14
12	0	5	0	0	0	0	0	0	0	0	0	0	5	8	7	0	1	7	5	7
Total	93	83	51	19	19	97	91	80	32	31	99	94	87	43	43	98	95	70	28	28

(7) and (8) respectively. Column 13 is the compound probability obtained from columns 3 and 4. Column 14 is obtained from column 6 and from the last part of Table II ($C_{\alpha+1,\beta} - C_{\alpha,\beta}$) as indicated by equation (11). The table for $C_{\alpha,\beta}$ is obtained from columns 7, 8, 9 and 13, using equations (9) and (10). The table for $C_{\alpha+1,\beta} - C_{\alpha,\beta}$ is obtained from the table for $C_{\alpha,\beta}$ by subtractions. These values are then used for column 14 according to equation (11). Column 15 is just the sum of elements of columns 11, 12 and 14. Column 16 is the same as the diagonal elements of $C_{\alpha,\beta}$. The elements of column 17 are the products of the elements of columns 6 and 16.

Table III gives the summarized results of the relative amounts of various sized particles deposited in different regions under selected conditions. It may be noted that for particles greater than one micron in diameter, the diameter may be replaced by $\sqrt{\rho}\, d$, so that density is directly accounted for except for very small particles. For small

TABLE IV

RELATIVE CONCENTRATION IN VARIOUS FRACTIONS OF THE EXPIRED AIR

Fraction of expired air	Particle Diameter in Microns 20	6	2	0.6	0.2
	300 cc/sec., 4 sec. cycle, 450 cc tidal air				
0-1/8	50	95	100	100	100
1/8-1/4	20	50	89	98	99
1/4-1/2	0	8	62	90	91
1/2-3/4	0	0	30	70	70
3/4-1	0	0	12	66	65
	300 cc/sec., 8 sec. cycle, 900 cc tidal air				
0-1/8	25	65	92	99	99
1/8-1/4	0	4	44	85	82
1/4-1/2	0	0	8	64	65
1/2-3/4	0	0	1	57	60
3/4-1	0	0	1	57	60
	300 cc/sec., 12 sec. cycle, 1350 cc tidal air				
0-1/8	10	50	80	97	97
1/8-1/4	0	0	20	75	70
1/4-1/2	0	0	5	55	56
1/2-3/4	0	0	5	54	54
3/4-1	0	0	0	33	36
	1000 cc/sec., 4 sec. cycle, 1500 cc tidal air				
0-1/8	15	40	84	98	98
1/8-1/4	0	0	57	82	82
1/4-1/2	0	0	23	75	75
1/2-3/4	0	0	20	70	71
3/4-1	0	0	6	56	55

particles of about 0.2 micron, the effect of settling is comparable to that of diffusion. The introduction of $d' = \sqrt{\rho}\, d$ as a new variable introduces d'^2 into S_α, but $\sqrt{1/d} = \sqrt{\sqrt{\rho}/d'}$ into D_α. Thus even for $\rho = 2$, $\rho^{1/4} = 1.2$; the error when both terms are comparable is about 10%. If the calculated retention is 30%, the correction would be only about 3% for $d = 0.2$ microns.

Table IV gives the relative concentrations of material in the various fractions of the expired air. These values are calculated from the values of $V_\alpha\, C_{1,\alpha}$. For example, the first entry in Table IV is obtained as follows: In Table II the sum of $V_\alpha\, C_{1,\alpha}$ for all α in the first 1/8 of the expired air [Mouth + Phar. + (0.045/0.06) Trachea] is 0.022 + 0.021 + 0.022. Thus the concentration is .065/(1/8) = 50%.

We next compare the results of these calculations with some available data (cf. Landahl and Herrmann, 1948). For corn oil droplets, the calculated values are somewhat too high in the neighborhood of fifty per cent retention, whereas for methylene blue particles, the calculated values are somewhat too low in the same range. For calcium phosphate dust, taken to be particles composed of packed spheres, the calculated values are appreciably higher than the observed values.

If sodium carbonate remained dry, its density should change the effective diameter by a factor of 1.5. But if the particles were all at equilibrium with completely saturated lung air, they should take up water to a diameter of about five times the original. Since the large particles may not have reached equilibrium, the effective factor to be applied to the diameter may not be constant. If a factor of two and one-half is applied, there is fairly satisfactory agreement at 18 and 60 liters per minute for the four second cycle, but not for the other cases. The comparison in these last cases is perhaps unjustified because of the hygroscopic property of the substance. Therefore, for the present, we may conclude that there is no serious discrepancy between these theoretical results and experimental data.

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THE STEADY STATE KINETICS OF SOME BIOLOGICAL SYSTEMS: III. THERMODYNAMIC ASPECTS

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Some thermodynamic aspects of steady systems are considered. The time rates of change, "flux," of various thermodynamic quantities are formulated. In particular the free energy flux in the steady state, the difference between the free energy flux in the steady and time dependent states and the change in free energy flux upon transition between steady states are discussed. Equations are derived which exhibit the formal similarities and differences between the free energy flux and the conventional free energy change. The temperature dependence of the steady state rate is examined and conditions for "mastery" by a single step discussed. A brief discussion of the role of *rate* in the coupling of exergonic and endergonic reactions is given.

Introduction. In two previous papers (Hearon 1949a & b, hereinafter referred to as I and II respectively) some aspects of the kinetics of steady state systems were discussed. In this work two matters, both of importance and interest, were not considered viz., the time course of the attainment of the steady state and the energetics of steady state processes. The former will be reserved for a subsequent paper now in preparation. The latter, which will be considered here, falls not strictly in the realm of formal kinetics. As will be seen, the problem of the energetics of steady state processes is intimately connected with the rate of the process. Thus the separation of the analysis into kinetics and energetics, while demanded in general by the strict adherence to the mechanical analogy, is logically faulty and of no use in practice.

We shall be interested here not only in computing the usual thermodynamic quantities for systems in which processes are proceeding at a finite and specified rate but also in the irreversible or dissipative aspects of such processes. The reasons for this emphasis are many. The computation, for example, of the irreversible production of entropy is of importance in principle and practice alike as has been discussed by R. C. Tolman and P. C. Fine (1948). The concept of irreversible entropy production or of the "uncompensated heat" of Clausius (De Donder, 1936; Van Rysselberghe, 1935; La Mer et al,

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1949) permits the second law of thermodynamics to be expressed as an equality. This is clearly an extension of the conventional formulation of some importance. The inclusion of the irreversible entropy in the first and second laws of thermodynamics is also of great practical importance from the standpoint of the discussion of the efficiency of thermodynamic processes as has been discussed in some detail (Tolman and Fine, 1948).

With the knowledge of the irreversible entropy production one can calculate in a simple manner the total rate of energy dissipation (a concept which is made precise in what follows) in a system in which irreversible processes are occurring. This quantity, in qualitative disguise, has entered biological theory at an early date.

Long ago A. J. Lotka suggested that " . . . . natural selection tends to make the energy flux through the system a maximum, so far as compatible with the constraints to which the system is subject." (Lotka, 1922.) This postulate and its logical basis are also carefully stated, respective of the restrictions that the supply of energy and matter not be limiting, in Lotka's book (Lotka, 1925) and have been discussed more recently elsewhere (Lotka, 1945, 1948). The term energy flux is defined explicitly (Lotka, 1922, p. 150, footnote 5) as " . . . . the available energy absorbed by and *dissipated* within the system per unit of time." (this author's italics).

N. Rashevsky (1943a) gave analytic form to the maximum principle of Lotka as a variational principle and subsequently (1943b) introduced a general Hamiltonian principle designed to care for the events of classical physics as well as those of biology. In application of this principle to the theory of amoeboid movement (1943c), cell division (1943d) and organization (1943d) by Rashevsky the term energy flux has taken on the meaning of energy exchange between biological units or between biological units and their environment. The quantity to be maximized is the total positive flow of energy. Dissipation of energy due to chemical reactions* is considered as a negative flow; flow from the system. Dissipation due to viscous forces which depend upon (generalized) velocities is cared for separately in the Hamiltonian principle (Rashevsky, 1943b). This would seem to be a rather different interpretation of flux of energy than Lotka's original definition. Furthermore in his most recent discussion Lotka (1948) introduces a slight change in point of view stating that " . . . . those species have the advantage which know best how to take *and put to favorable use* the stream of energy available in nature.

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*The dissipation term used by Rashevsky to account for (spontaneous) chemical reactions is quite different formally and conceptually from that discussed in IV following (p. 86).

Collectively this will tend to increase the flux of energy through the system, which flux may thus be said to be approaching a maximum." (Lotka's italics). This implies that *efficiency* plays a definite role.*

The point of this somewhat lengthy discussion is to exhibit the importance, in general biological theory, of the dissipative aspects of energetics. The question of the relative roles of energy flow or exchange of dissipation and of efficiency in an adequate maximal principle, if such be possible, is an involved one: we eschew it here. It is pointed out, however, that the question of the possibility of such a maximal principle in biology was a factor in the initiation of the present investigation. Further we submit that the thermodynamically acceptable form for the quantities required for such a formulation, i.e., dissipation, rate of change of free energy, etc., are available in the results of this paper and the more general formulations of irreversible processes to be referred to in IV.

The results to be considered divide naturally into two groups: 1) The formulation of the various energetic quantities for systems which are homogeneous and in which chemical processes are occurring at a specified rate. These results are presented here. 2) Similar formulations for non-homogeneous systems (systems in which there are spacial gradients of composition), for geometrically confined regions, such as the cell, and their associated diffusion fields. These are presented in part IV. The above corresponds to the division of purely kinetic topics into those discussed in I and II respectively.

Closed, Homogeneous Systems.

In this part we will discuss the general set of consecutive reactions considered in I and II; familiarity with these papers is presupposed. We regard the system as closed and hence exclude the interchange of matter between the system and environment. The constancy of the concentrations of the reactants, $[C_i]$, and of the products, $[B_i]$, is thus supposed to be cared for in one of the ways previously discussed. The manner in which the following problems are formulated in general will depend upon the information available and upon the conditions imposed. For any given set of conditions it is well known that there exists a characteristic function giving rise to what J. W. Gibbs (1928) termed a fundamental equation. It is also well known that knowledge of this characteristic thermodynamic function and the fundamental equation allows the derivation of all other thermodynamic properties of the system. The

*That Lotka had not previously ignored the factor of efficiency is evident in an addendum to the 1922 article. The reader is referred to this and to Lotka (1925) for his arguments on this point.

conditions of most general interest are those of constant temperature and pressure. The point of departure will thus be to choose the Gibbs' function or free energy, F, as the characteristic function. Furthermore for isothermal processes the irreversible entropy production is most simply obtained from the free energy change. It will be necessary to assume as available extra-thermodynamic information in the form of the rate constants and their temperature dependence. Otherwise, however, the formulations are entirely within the framework of classical thermodynamics, a feature which is discussed at the close of this paper.

The free energy will be taken as a function of the temperature, T, the pressure, P, and the composition which is specified by n_i, $i = 1, 2 \ldots.$, the number of moles of the ith constituent. The familiar differential, at constant T and P, is

$$dF = \sum_k \mu_k dn_k, \tag{1}$$

where the μ_k are the chemical potentials $\left(\frac{\partial F}{\partial n_k} \right)_{T,P,n_j}$ $j \neq k$. They are taken to be of the form

$$\mu_k = \mu_k{}^0 + RT \ln C_k, \tag{2}$$

where $\mu_k{}^0$ is the standard chemical potential of the kth solute, a function only of T and P when the solvent is specified; C_k is the concentration of the kth solute. Relation (2) embodies the usual assumptions (Guggenheim, 1930, 1936) regarding perfect dilute solutions; in what follows the modifications necesary when these assumptions no longer hold will be noted at the appropriate time.

Time Rate of Change of F.

For the chemical reaction

$$-\nu_1 R_1 - \nu_2 R_2 = \nu_3 P_3 + \nu_4 P_4 \tag{3}$$

one may, following Th. De Donder (1936), define the quantity ξ by

$$dn_i = \nu_i d\xi . \tag{4}$$

The ν_i are the number of moles of the ith constituent *produced* in the reaction (3) as written. The quantity ξ is the extent of the reaction (see also Mayer and Mayer, 1940; MacDougall, 1939). If the dn_i from (4) are substituted into (1) we obtain

$$\frac{\partial F}{\partial \xi} = \sum_k \nu_k \mu_k . \tag{5}$$

The time rate of change of the free energy is given by

$$\frac{dF}{dt} = \left(\frac{\partial F}{\partial \xi}\right)\frac{d\xi}{dt} = \left(\sum_k \nu_k \mu_k\right)\frac{d\xi}{dt}. \tag{6}$$

The quantity $\frac{d\xi}{dt}$ is the rate of the reaction in the sense that

$$\frac{d\xi}{dt} = \frac{d(n_i/\nu_i)}{dt}. \tag{7}$$

Thus $d\xi/dt$ is the time rate of change of the number of equivalents, n_i/ν_i, of any constituent and is easily expressed in terms of more familiar chemical kinetic expressions. The quantity $\sum_k \nu_k \mu_k$ is the free energy of the reaction. It is frequently written simply as ΔF to designate the change in free energy, per equivalent, of the reaction; it is actually the slope at any point of the F vs. ξ curve. When the μ_k from (2) are substituted into (6) the concentration values must then be the instantaneous values. If several reactions are to be considered, a ξ_j is defined for each reaction and the equations corresponding to (5) and (6) are obtained by summing over j. Implicit in (5) and (6) is the assumption that the mechanism of the overall reaction is correctly portrayed by (3): There can be no intermediate steps or reactions and the disappearance of ν_1 and ν_2 moles of R_1 and R_2 must be strictly accompanied by the appearance of ν_3 and ν_4 moles of P_3 and P_4.

The expression such as (6) for the set of reactions discussed in I may be derived, taking into account that there are many steps and that every X_i participates in at least two such steps, as follows: Since every $|\nu_i|$ is one, there is no distinction between equivalents and moles. Consider the ith step

$$X_{i-1} + C_i \leftrightarrows X_i + B_i.$$

The free energy change per mole is ΔF_i and the rate (moles/volume/time) is v_i. The rate of change of the free energy for the ith step, *per unit volume,* is thus $\Delta F_i\, v_i$ and for the complete set of reactions

$$\frac{dF}{dt} \equiv \boldsymbol{F}(t) = V \sum_k \Delta F_k v_k, \tag{8}$$

where V is the total volume of the system. The dimensions of $\boldsymbol{F}(t)$ are energy/time and the units will usually be calories/sec. Denote by $[X_k]$ the concentration of X_k when the system is in a time-dependent state and by $[X_k^s]$ the concentration when the system is in the steady state. (Note that in I $[X_k]$ signified the steady state value with no qualifying notation for only steady state systems were discussed there.) Using the notation of I with the above modification,

$$\Delta F_k = RT\, ln\, \frac{w_{-k}[X_k]}{w_k[X_{k-1}]}, \tag{9}$$

where by definition,

$$[X_0] = [X_n] \equiv 1\,. \tag{10}$$

For v_k we have

$$v_k = w_k[X_{k-1}] - w_{-k}[X_k]\,. \tag{11}$$

Expression (9) is easily seen to be identical with [recall equations (1) of I]

$$\left.\begin{aligned} \Delta F_k &= \mu_{B_k} + \mu_{X_k} - (\mu_{C_k} + \mu_{X_{k-1}}) \\ &= \Delta F_k{}^0 + RT\, ln\, \frac{[B_k][X_k]}{[C_k][X_{k-1}]}, \end{aligned}\right\} \tag{12}$$

when it is recalled that

$$\left.\begin{aligned} \mu_{B_k}{}^0 + \mu_{X_k}{}^0 - (\mu_{C_k}{}^0 + \mu_{X_{k-1}}{}^0) &\equiv \Delta F_k{}^0 \\ &= -RT\, ln\, K_k\,, \end{aligned}\right\} \tag{13}$$

and that the μ's are given by (2). Equation (8) with ΔF_k from (9) and v_k from (11) yields

$$\boldsymbol{F}(t) = V \sum_k (w_k[X_{k-1}] - w_{-k}[X_k])\, RT\, ln\, \frac{w_{-k}[X_k]}{w_k[X_{k-1}]}. \tag{14}$$

Equation (14) correctly accounts for the fact that every X_k is produced in the kth step at the rate v_k and is consumed, at a different rate, v_{k+1}, in the subsequent, $(k+1)$st, step and that although the production and consumption occur at the same instantaneous value of $[X_k]$ the ΔF's of the kth and $(k+1)$st steps are in general different.

Rate of Change of F *in Steady State.*

When the system is in the steady state the value of $\boldsymbol{F}$ is no longer time dependent and is denoted as $\boldsymbol{F}_s$. Further for every k

$$\left.\begin{aligned} [X_k] &= [X_k{}^s]\,; \\ v_k &= v_s\,. \end{aligned}\right\} \tag{15}$$

Equations (11) with (15) lead to the set (2) of I and v_s is the steady state velocity discussed in I and designated there as v.

Equation (14) then becomes

$$\left.\begin{aligned} F_s &= V\left(\sum_{k=1}^{n} RT\, ln \frac{w_{-k}}{w_k}\right) v_s \\ &= V\, \Delta F\, v_s\, . \end{aligned}\right\} \tag{16}$$

Equation (16) is readily verified by noting that

$$\left.\begin{aligned} \sum_{k=1}^{n} ln \frac{[X_k]}{[X_{k-1}]} &= ln\left[\prod_{k=1}^{n} [X_k] \prod_{k=1}^{n} \frac{1}{[X_{k-1}]}\right] \\ &= ln\left[\prod_{k=1}^{n} [X_k] \prod_{j=1}^{n} \frac{1}{[X_j]}\right] = 0\, , \end{aligned}\right\} \tag{17}$$

where in (17) the definitions (10) have been used in effecting the change of index. It is clear that in (16), ΔF, the free energy change of the overall reaction, is, because of equations (1) of I and (17):

$$\left.\begin{aligned} \Delta F &= \sum_{k} \Delta F_k \\ &= \Delta F^0 + RT\, ln \frac{[B_1][B_2] \cdots\cdot [B_n]}{[C_0][C_1] \cdots\cdot [C_n]}\, , \end{aligned}\right\} \tag{18}$$

where

$$\left.\begin{aligned} \Delta F^0 &= -RT\, ln\, K = -RT\, ln \prod_{k=1}^{n} K_k \\ &= \sum_{k} \mu_{B_k}{}^0 - \sum_{k} \mu_{C_k}{}^0\, , \end{aligned}\right\} \tag{19}$$

which is the conventional but less useful form. So long as the system is in the steady state the change in free energy per unit time has the constant value F_s; it can be shown in a simple manner that this is always a negative quantity. Equation (16) is written, for this purpose, in the form

$$F_s = V\left(RT\, ln \frac{\prod_k w_{-k}}{\prod_k w_k}\right)\left(\frac{\prod_k w_k - \prod_k w_{-k}}{\phi}\right)\, . \tag{20}$$

The last factor in (20) is v_s from equation (3) of I with ϕ as defined in equation (18) of II: ϕ is a sum of positive terms [eq. (21) of II]. The second factor in (20) is ΔF from (16). If

$$\prod_k w_k > \prod_k w_{-k}\, , v_s > 0 \text{ and } \Delta F < 0\, , \tag{21}$$

and if

$$\mathop{\Pi}_{k} w_k < \mathop{\Pi}_{k} w_{-k}\ ,\ v_s < 0 \text{ and } \Delta F > 0\,, \tag{22}$$

thus $\mathbf{F}_s \leq 0$ under all conditions, the equality holding for the equilibrium condition. Similarly $\mathbf{F}(t)$ is always negative, for by the same reasoning every $\Delta F_k\ v_k$ in (8) is negative as can be seen from (9) and (11). In words, if the first inequality of (21) is satisfied, the steady state rate is positive and the last equality shows that the process is spontaneous. If the first inequality of (22) is satisfied, the B_i are converted to the C_i: ΔF for the reaction *as written* is positive, but the process proceeds in the direction of spontaneity for the *reverse* of the reaction as written takes place. From the above it is clear that $\Delta F = 0$ is a sufficient condition for $v_s = 0$. For the system discussed it is also a necessary condition; the vanishing of v_s necessarily implies that $\Delta F = 0$. In general however this last statement is not true. Is should be made clear that although we have regarded every $[C_i]$ and $[B_i]$ and hence every w_i and w_{-i} as constant, the conclusions $\mathbf{F}_s \leq 0$, $\mathbf{F}(t) \leq 0$ drawn from (21) and (22) do not depend upon this condition. What we have done is to admit the net conversion of the C_i to the B_i but not admit changes in these concentrations. If one considers an open system by requiring that the $[C_i]$ and $[B_i]$ are maintained constant in the system proper by flow from and to the environment (see discussion in II), *then* in the steady state there is no net production of any C_i, B_i, or X_i. For such a system the condition, cf. the second equality of (18), that the difference in chemical potentials of the products and reactants (which we will call the potential difference) in the system is zero* is a sufficient condition for the vanishing of every rate, $\dfrac{\partial[C_i]}{\partial t}$, $\dfrac{\partial[B_i]}{\partial t}$, $\dfrac{\partial[X_i]}{\partial t}$; it is *not* a necessary condition for every rate may vanish without necessarily implying that the potential difference is zero. For X_k,

$$\begin{aligned}\frac{d[X_k]}{dt} &= (w_k[X_{k-1}] - w_{-k}[X_k]) - (w_{k+1}[X_k] \\ &\quad - w_{-(k+1)}[X_{k+1}]) = v_k - v_{k+1}\,;\end{aligned} \tag{23}$$

the rate vanishes if v_k and v_{k+1} vanish separately: This is the condition of equilibrium and the potential difference is zero. The rate also vanishes if $v_k = v_{k+1}$, this is the steady state and the potential difference is *not* zero.

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*Note that this condition can be attained when and only when the (fixed) environmental concentrations are such that the equilibrium condition may be satisfied. Similarly the closed system discussed here can come to equilibrium *only* if the w's are arranged to satisfy the equilibrium ratio unless the condition of constancy be relaxed for some of them.

It is in fact true that when such an open system is in the steady state *every extensive property of the system is time independent.* There is no time rate of change of F in the system but only in the environment. This is of considerably more importance in the topics discussed in IV.

C. Eckart (1940, see addendum p. 924) has given a rather detailed proof of what is equivalent to our propositions $\boldsymbol{F}(t) \leq 0$, $\boldsymbol{F}_s \leq 0$ and discussed whether the usual kinetic rate formulae are in accord with the general thermodynamic principles discussed in his paper: Both the proof mentioned and demonstration that the formal kinetic rate laws are in accord with general thermodynamic principles are based on expressing any concentration as

$$[C_i] = \exp\{(\mu_i - \mu_i^0)/RT\}\,. \tag{24}$$

Inherent in the rate laws used by him is the fact that

$$\sum_i \nu_i \mu_i^0 = -RT \ln K; \tag{25}$$

cf. equations (13) and (19) of this paper. It seems necessary to only mention this here especially in view of the fact that the absolute reaction rate theory (Glasstone et al, 1941), as opposed to classical collision theory, brings kinetic rate theory into complete accord with general thermodynamic principles. Later it will be pointed out that De Donder (1936) has already given a theorem which will be shown to be equivalent to $\boldsymbol{F} \leq 0$.

It is worth mentioning that the set of reactions discussed in I and II is not very general in its stoichiometry, i.e., every $|\nu_i| = 1$ as mentioned. The modifications of what has been formulated here for a different stoichiometry are simple and obvious. The reactions can be made as general as is necessary: There may be any number of B's or C's in any step or there may be two of a given C_j, in which case the square of $[C_j]$ appears in w_j. The only restriction is that each step be first order with respect to the X's involved, for only then is the steady state solution given in I valid. Be this as it may the set of reactions was intentionally set up in this manner. For it is regarded as most improbable that a single step be of more than second order. It is well known that three-body complexes are formed in many catalytic systems of biological importance but they are formed stepwise by first and second order reactions.

The Difference $\mathbf{F}(\mathrm{t}) - \mathbf{F}_s$.

It is of some interest to inquire as to possible extremal properties of $\boldsymbol{F}_s$, i.e., whether $\boldsymbol{F}$ under steady state conditions is always greater or always less than under variable state conditions. To anticipate a later discussion it may be stated that this will also answer the same question regarding the rate of dissipation. It can be shown from (14) that the $\partial \boldsymbol{F}/\partial [X_k]$ vanish simultaneously only if the conditions of equilibrium, $v_k = 0$ for all k, obtain. The difference, $\boldsymbol{F}(t) - \boldsymbol{F}_s$ which may be positive, negative or zero is given by

$$\frac{\boldsymbol{F}(t) - \boldsymbol{F}_s}{V} = \sum_k \Delta F_k (v_k - v_s) . \tag{26}$$

Equation (26) results from (8) and (16); the ΔF_k are to be taken from (9). The result may be expressed as in (26) because the addition, to (16), of RT times (17) changes nothing whether or not the $[X_k]$ are steady state values. Certain forms of (26) are of interest. Substitution of (9) into (26) gives

$$\frac{\boldsymbol{F}(t) - \boldsymbol{F}_s}{V} = \sum_{k=1}^{n} \left(RT\, ln \frac{w_{-k}}{w_k} \right) (v_k - v_s) + \sum_{k=1}^{n} \left(RT\, ln \frac{[X_k]}{[X_{k-1}]} \right) v_k . \tag{27}$$

Because of (10) the last summation in (27) can be written

$$\sum_{k=1}^{n} (RT\, ln [X_k]) (v_k - v_{k+1}) . \tag{28}$$

Now the rate of change of $[X_k]$ is, from (23),

$$\begin{aligned} \frac{d[X_k]}{dt} &= w_k [X_{k-1}] - (w_{-k} + w_{k+1}) [X_k] \\ &+ w_{-(k+1)} [X_{k+1}] , \end{aligned} \tag{29}$$

or, in terms of the displacements from the steady state values,

$$\begin{aligned} \frac{d\Delta X_k}{dt} &= w_k\, \Delta X_{k-1} - (w_{-k} + w_{k+1}) \Delta X_k \\ &+ w_{-(k+1)}\, \Delta X_{k+1} \equiv \dot{\Delta X}_k , \end{aligned} \tag{30}$$

where

$$\Delta X_k \equiv [X_k] - [X_k^s] . \tag{31}$$

But from (23), (29) or (30) is an expression for $v_k - v_{k+1}$. Also

$$v_k - v_s = w_k\, \Delta X_{k-1} - w_{-k}\, \Delta X_k . \tag{32}$$

Putting equations (28), (30), (31) and (32) into (27) gives

$$\left.\begin{aligned}\frac{\boldsymbol{F}(t)-\boldsymbol{F}_s}{V}=&\sum_{k=1}^{n}\left(RT\ ln\frac{w_{-k}}{w_k}\right)\left(w_k\,\Delta X_{k-1}-w_{-k}\,\Delta X_k\right)\\&+\sum_{k=1}^{n}\left[RT\ ln([X_k{}^s]+\Delta X_k)\right]\dot{\Delta X}_k.\end{aligned}\right\}\tag{33}$$

The definition (10) gives, of course,

$$\Delta X_0=\Delta X_n\equiv 0\,.\tag{34}$$

Equation (33) involves only steady state values of the $[X_k]$ obtainable from equation (6) or (7) of I and the ΔX_k obtainable from the solution of the set (30). Because of (34), explicit introduction of $\dot{\Delta X}_k$ from (30) into (33) gives*

$$\frac{\boldsymbol{F}(t)-\boldsymbol{F}_s}{V}=\sum_{k=1}^{n}\Delta X_k\,(w_{-k}\,\Delta F_{-k}+w_{k+1}\,\Delta F_{k+1})\tag{35}$$

in which ΔF_k is to be taken from (9) and, of course,

$$\Delta F_k=-\Delta F_{-k}\,.\tag{36}$$

By (31), (35) can be expressed in terms of the $[X_k{}^s]$ and the ΔX_k; as it stands it involves the time dependent X-concentrations and the ΔX_k. As a simple example the case $A \leftrightarrows X_1 \leftrightarrows B$ will be discussed. Using the form (35)

$$\begin{aligned}&\frac{\boldsymbol{F}(t)-\boldsymbol{F}_s}{V}\\&=-k_{-1}\,\Delta X_1\left(RT\ ln\frac{[X_1]}{K_1[A]}\right)+k_2\,\Delta X_1\left(RT\ ln\frac{[B]}{K_2[X_1]}\right).\end{aligned}\tag{37}$$

The solution of (30) for ΔX_1 is

$$\Delta X_1=\Delta X_1{}^0\,e^{-at},\tag{38}$$

where $a\equiv k_{-1}+k_2$ and $\Delta X_1{}^0=[X_1]^0-[X_1{}^s]$ is the initial displacement from the steady state. Equation (37) vanishes for very large t when $\Delta X_1\rightarrow 0$; it also vanishes for

$$[X_1]=\frac{(K_1[A])^{k_{-1}/a}}{(K_2/[B])^{k_2/a}}.\tag{39}$$

From (39) it is seen that

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*Note that (35) may be formed by taking the "self term" of (29), multiplying each w by the corresponding ΔF and summing.

$$\left.\begin{array}{ll}\text{if} \quad k_{-1} >> k_2, & [X_1] \sim K_1[A]; \\ \text{if} \quad k_{-1} << k_2, & [X_1] \sim [B]/K_2. \end{array}\right\} \tag{40}$$

Under *these* conditions (37) vanishes when the first or second step passes through the equilibrium position. For the $[X_1]$ values in (40) are approximately equilibrium values but clearly the two conditions in (40) are mutually exclusive. The time at which (37) vanishes, other than $t = \infty$, is

$$t = -\frac{1}{a} \ln \frac{\Delta X_1}{\Delta X_1{}^0}. \tag{41}$$

From (38) ΔX_1 and $\Delta X_1{}^0$ must have the same sign, further $|\Delta X_1{}^0| > |\Delta X_1|$, thus t from (41) is real and finite, for $1/a$ is inherently positive, and at this time (37) vanishes as well as at very large t.

For more complex cases the ΔX_k from (30) are of the form

$$\Delta X_k = \sum_{j=1}^{n-1} a_{kj}\, e^{-\lambda_j t}, \tag{42}$$

and the analysis is not so simple for the ΔX_k themselves need not be monotone in t (Burton, 1939) a matter which will be discussed in V of this series. It is of interest to note for the simple system discussed here that "overshoot" in a thermodynamic quantity is possible when the concentration $[X_1]$ is capable of no "overshoot."

Change in $\mathbf{F}_s$, *Upon Transition*

The expression for the change in $\boldsymbol{F}_s$ between one steady state and another will depend upon what has induced the transition between steady states. If any of the $[B_i]$ or $[C_i]$ be changed both v_s and the potential factor, what we have called the potential difference, given by (18), will usually change; only one part of the potential factor will change for ΔF^0 is independent of concentration. If one imagines one or more rate constants to be changed, v_s is changed and only ΔF^0 of the potential factor is changed. Finally if a given C_j is conserved in the system, such as is true of catalysts (see I), then there is some B_m, $m > j$, which is identical with C_j. The concentration of this component may enter into v_s in a complicated manner (cf. I) but its concentration always cancels from the potential factor as is obvious from (18). Thus if the concentration of a catalyst be changed, *only* v_s is changed. These cases may be indicated as follows: In (18) denote the concentration ratio in ΔF by R_n. Thus R_n is the "product to reactant ratio" for an n-step system. Then (16) becomes

$$\boldsymbol{F}_s = V[\Delta F^0 + RT \ln R_n]\, v_s. \tag{43}$$

If any non-catalytic $[B_i]$ or $[C_i]$ be changed:

$$\frac{\boldsymbol{F}_{s2}-\boldsymbol{F}_{s1}}{V} = \Delta F^0 (v_{s2}-v_{s1}) + v_{s2}\, RT \ln R_{n2} - v_{s1}\, RT \ln R_{n1} . \tag{44}$$

If any rate constant k_i or k_{-i} be changed:

$$\frac{\boldsymbol{F}_{s2}-\boldsymbol{F}_{s1}}{V} = \Delta F_{(2)}{}^0\, v_{s2} - \Delta F_{(1)}{}^0\, v_{s1} + (v_{s2} - v_{s1}) RT \ln R_n . \tag{45}$$

If any catalytic or conserved $[C_i]$ be changed:

$$\frac{\boldsymbol{F}_{s2}-\boldsymbol{F}_{s1}}{V} = (\Delta F^0 + RT \ln R_n)(v_{s2}-v_{s1}) . \tag{46}$$

Equations (44), (45) and (46) give the excess of rate of expenditure of free energy, per unit volume, for the second steady state over that for the first steady state when the transition is induced by the agency indicated. The subscripts 1 and 2 refer to the respective steady states; quantities with no such subscript are identical in the two states. Equation (46) applies not only to the change in concentration of enzymes but also to the change in concentration of many metabolites which function cyclicly and are conserved. The role of such cyclic processes has been discussed in great detail by H. A. Krebs (1948). The difference in free energy between the two states may be obtained by

$$F_2 - F_1 = \int_{t_1}^{t_2} \boldsymbol{F}(t)\, dt , \tag{47}$$

where t_1 is the time at which the transition was initiated and t_2 is a time chosen such that the new steady state is approached with any degree of approximation, since in principle the transition takes forever. It seems of doubtful value to attempt to carry (47) further in any general case. For that matter it is the heat change between two such states which is experimentally amenable and of interest.

Time rate of Change of H *and* S .

Thus far we have confined the discussion to the quantity $\boldsymbol{F}$. A thorough treatment of the subject, some aspects of which are being discussed here, would exhibit the derivation for a steady state system and for a system approaching such a state the counterpart of all the usual qualities discussed for equilibrium reactions or for other processes, not withstanding the time factor. Actually not all counterparts exist; of those which do, not all are of value or interest. As mentioned it is a familiar procedure to derive from a characteristic function and its fundamental equation the remaining thermodynamic functions.

It will be shown here what results when this same procedure is adapted formally for the function $\mathbf{F}_s$. This will lead naturally to the time rate of change of other thermodynamic functions and will raise in a definite manner the question of the temperature dependence of v_s. This latter question will be treated. In the first place it is evident from (16) that if

$$\frac{\partial[f(x)\cdot F]}{\partial x} = Y, \qquad (48)$$

Y being the partial derivative of the product of any function $f(x)$, of some parameter x, and the free energy F with respect to the parameter x, then it is true that

$$\frac{\partial[f(x)\cdot \mathbf{F}]}{\partial x} = \mathbf{Y} + f(x)\cdot \mathbf{F}\frac{\partial \ln v_s}{\partial x}. \qquad (49)$$

The quantity $\mathbf{Y}$ is

$$\mathbf{Y} \equiv \frac{dY}{dt} = V \Delta Y v_s, \qquad (50)$$

where ΔY is the change in Y for the overall reaction; Y will here be some extensive property of the system but this need not be true in general. For want of a better terminology we will call $\mathbf{Y}$ the Y-flux. Thus $\mathbf{F}$, $\mathbf{H}$, $\mathbf{S}$, $\mathbf{E}$, etc. are the free energy-flux, enthalpy-flux, *total* entropy-flux, energy-flux, etc. Some examples of (49) are

$$\frac{\partial \mathbf{F}_s/T}{\partial T} = -\frac{\mathbf{H}}{T^2} + \frac{\mathbf{F}_s}{T}\frac{\partial \ln v_s}{\partial T}; \qquad (51)$$

$$\frac{\partial \mathbf{F}_s}{\partial T} = -\mathbf{S} + \mathbf{F}_s\frac{\partial \ln v_s}{\partial T}; \qquad (52)$$

$$\frac{\partial \mathbf{F}_s}{\partial P} = \tilde{\mathbf{V}} + \mathbf{F}_s\frac{\partial \ln v_s}{\partial P}. \qquad (53)$$

The quantity $\Delta\tilde{V}$ is the change in volume accompanying the overall reaction

$$\Delta\tilde{V} = \sum_{i=1}^{n} \tilde{V}_{B_i} - \sum_{i=0}^{n} \tilde{V}_{C_i}.$$

In taking V the volume of the system as fixed we have regarded ΔV as negligibly small which it, in fact, usually is though it is determinable from the P-dependence of F. An alternative form of (51) is

$$\frac{\partial \boldsymbol{F}_s/T}{\partial 1/T} = \boldsymbol{H} + \frac{\boldsymbol{F}_s}{T}\frac{\partial \ln v_s}{\partial 1/T}; \tag{54}$$

the derivative in the last term of (54) is a familiar one in the study of rates in their temperature dependence.

The total entropy-flux and enthalpy-flux may be discussed briefly as follows. By the general definition (50)

$$\boldsymbol{S} = V \Delta S\, v_s . \tag{55}$$

By carrying out the differentiation indicated in (52) it is seen that

$$\boldsymbol{S} = V(\Delta S^0 - R \ln R_n) v_s , \tag{56}$$

where R_n has the significance discussed in connection with (43) and

$$\frac{\partial \Delta F^0}{\partial T} = -\Delta S^0. \tag{57}$$

By using the familiar $\Delta F^0 = \Delta H^0 - T\Delta S^0$ and (19), equation (56) may be put in the form

$$\boldsymbol{S} = V\left(\frac{\Delta H^0}{T} - \sum_k R \ln \frac{w_{-k}}{w_k}\right) v_s , \tag{58}$$

comparable to (16). Similarly

$$\boldsymbol{H} = V \Delta H\, v_s \tag{59}$$

gives the heat absorbed per unit time. The heat absorbed in the transition from one steady state to another is given by

$$H_2 - H_1 = \int_{t_1}^{t_2} \boldsymbol{H}(t)\, dt , \tag{60}$$

where the limits of the integral (60) are as discussed for (47). It would be of great interest to investigate the usefulness of (60) in problems such as "heat of shortening" (Hill, 1949) in which the situation is exactly the transition from one steady rate of heat evolution to another. Because we have considered perfect dilute solutions, the values of ΔH and $\boldsymbol{H}$ are identical with the corresponding standard quantities ΔH^0 and $\boldsymbol{H}^0$, but we have not used this fact. If activity coefficients are inserted into the w's the following change must be made: there will appear in (56) the additive term

$$R\frac{\partial\, ln\, \gamma_n}{\partial T}, \tag{61}$$

where γ_n is the ratio of activity coefficients formed as in R_n; in (58) ΔH will appear in place of ΔH^0; ΔH in (59) will be

$$\Delta H^0 + R\frac{\partial\, ln\, \gamma_n}{\partial\, 1/T}. \tag{62}$$

There is one further derivative which should be mentioned, viz.,

$$\frac{\partial \boldsymbol{F}_s}{\partial[C_i]} = -v_s\frac{V R T}{[C_i]} + \boldsymbol{F}_s\frac{\partial\, ln\, v_s}{\partial[C_i]}. \tag{63}$$

In general with v_s from (3) of I, (63) is not simple. From (16) it follows that if any $w_{-k} = 0$, $\Delta F = -\infty$. It is possible however for the overall reaction to be irreversible so far as v_s is concerned and still have ΔF maintain its form. In short $\underset{k}{\Pi}\, w_k$ may be neglected with respect to $\underset{k}{\Pi}\, w_{-k}$ and ΔF by no means be infinite. In fact the reaction can be considered as irreversible for values of the w's which permit no terms to be dropped from ΔF. For example then let $w_{-n} = 0$. Taking v_s from (24) of II there is obtained

$$\frac{\partial\, ln\, v_s}{\partial[C_i]} = \frac{\Phi_i\, v_s}{V_m^{(C_i)}[C_i]^2}. \tag{64}$$

Eliminating Φ_i, because it is less simple to construct (see II) than $V_m^{(C_i)}$ by using (24) of II, (63) becomes,

$$\frac{\partial \boldsymbol{F}_s}{\partial[C_i]} = \frac{1}{[C_i]}\{\boldsymbol{F}_s(1 - v_s/V_m^{(C_i)}) - V\, v_s\, \boldsymbol{RT}\}. \tag{65}$$

T-*dependence of* v_s.

In (51) and (52) and (54) there arises the temperature derivative of v_s. Having given (56), (58) and (59) for $\boldsymbol{S}$ and $\boldsymbol{H}$ it remains to complete (51), (52) and (54) by exhibiting explicitly the T-dependence of v_s. This is in itself an important problem in steady state kinetics and it may be anticipated that the expression will involve a large number of thermodynamic quantities. It is commonplace in biology to assume that the T-dependence of v_s is determined by the thermal characteristics of the slowest step in the sequence provided only that it is sufficiently slower than all other steps. This assumption is tantamount to the assumption that the expression for the overall rate, v_s, is that for the slowest step. This assumption is true only if other conditions are met as is apparent from the discussion in I; further, it is by no means confined to biology (Glasstone et al, 1941, 199; Branch and Calvin, 1941, 375). It will be seen that in general the T-dependence of v_s involves the standard heat of the overall reaction, ΔH°, the standard heats, ΔH_k°, of the individual steps and every standard heat of activation, $\Delta H_k\ddagger$, of the forward rates. The general expression is unwieldy and it is a separate problem, pursued to no great extent here, to assess the various permissible approximations. We begin by dividing numerator and denominator of equation (3) of I by $\underset{k}{\Pi}\, w_k$, obtaining v_s in the form (66) which contains the maximum number of equilibrium constants and the minimum number of individual rate constants all of which refer to *forward* steps, viz.,

$$v_s = \frac{1 - R_n/K}{\sum_{k=1}^{n} A_k}, \tag{66}$$

where R_n and K have already been defined, [see (18) and (43)-(46)]. The A_k are additive terms, T_k, [equation (21) of II] of ϕ, equations (18) of II and (20) of this paper, divided by $\underset{k}{\Pi}\, w_k$. They may be written as

$$\left.\begin{aligned} A_k &= \left(\prod_{j=1}^{k-1} k_j^{-1}\right)\left(\prod_{j=1}^{k-1} \frac{[B_j]}{[C_j]}\right)\frac{1}{w_k} \\ &= \frac{R_{k-1}}{K_{1,k-1}}\,\frac{1}{w_k}; \\ &K_{1,k-1} \equiv 1 \quad \text{if} \quad k = 1, \end{aligned}\right\} \tag{67}$$

where R_{k-1} is the "product to reactant ratio," constructed as R_n, for the first $k - 1$ steps and $K_{1,k-1}$ is the overall equilibrium constant for the steps 1 through $k - 1$ as is clear from (67). From (66) are obtained

$$\frac{\partial v_s}{\partial T} = \frac{\left(\sum_k A_k\right)\frac{\partial}{\partial T}\left(-R_n/K\right) + \left(R_n/K - 1\right)\frac{\partial}{\partial T}\sum_k A_k}{\sum_j \sum_k A_j A_k}, \tag{68}$$

and

$$\frac{\partial \ln v_s}{\partial T} = \frac{-\dfrac{\partial}{\partial T}(R_n/K)}{1 - R_n/K} - \frac{\dfrac{\partial}{\partial T}\sum A_k}{\sum\limits_k A_k}. \tag{69}$$

Equation (68) or (69) may be simplified as follows:

$$\frac{\partial}{\partial T}(R_n/K) = -\frac{R_n}{K}\,\frac{\Delta H^0}{R\,T^2}, \tag{70}$$

where ΔH^0 has been defined and we have used the well known relation,

$$\frac{\partial \ln K}{\partial T} = \Delta H^0/RT^2. \tag{71}$$

Also

$$\frac{\partial A_k}{\partial T} = \frac{R_{k-1}}{w_k}\,\frac{\partial\, 1/K_{1,k-1}}{\partial T} - \frac{R_{k-1}}{K_{1,k-1}}\,\frac{1}{w_k}\,\frac{\partial \ln w_k}{\partial T}, \tag{72}$$

and from (71)

$$\frac{\partial\, 1/K_{1,k-1}}{\partial T} = -\frac{\Delta H^0_{1,k-1}}{K_{1,k-1}\,RT^2}, \tag{73}$$

where $\Delta H^0_{1,k-1}$ is the standard heat of reaction for the steps 1 through $(k-1)$ and in view of the make up of $K_{1,k-1}$ from (67) is, of course,

$$\begin{aligned} \Delta H^0_{1,k-1} &= \sum_{j=1}^{k-1} \Delta H_j^0\,, \quad && k > 1 \\ &= 0 && k = 1. \end{aligned} \tag{74}$$

Finally since w_k is a forward rate constant multiplied by concentration terms, with the usual approximation,* (Glasstone et al, 1941)

$$\frac{\partial \ln w_k}{\partial T} = \Delta H_k^{\ddagger}/RT, \tag{75}$$

where $\Delta H_k^{\ddagger}$ is the standard heat of activation of the forward kth step. Using (73) and (75) in (72) gives

$$\frac{\partial A_k}{\partial T} = -A_k\left\{\frac{\Delta H^0_{1,k-1} + \Delta H_k^{\ddagger}}{RT^2}\right\}. \tag{76}$$

*Strictly $k_i = \left(\frac{kT}{h}\right) \exp\{-\Delta F_i{\ddagger}/RT\}$ with k the Boltzman and h Planck's constant, the variation of $\ln T$ relative to $1/T$ is neglected. This is usually done (Glasstone et al, 1941).

Substitution of (70) and (76) into (69) gives

$$\frac{\partial \ln v_s}{\partial 1/T} = \frac{-\Delta H^0/R}{K/R_n - 1} - \frac{\sum_k A_k(\Delta H^0_{1,k-1} + \Delta H_k^\ddagger)/R}{\sum_k A_k}. \tag{77}$$

It is easily seen that if the overall reaction is irreversible, say, because $w_{-n} \sim 0$ then (66) gives

$$v_s = 1/\sum_k A_k, \tag{78}$$

and (77) becomes

$$\frac{\partial \ln v_s}{\partial 1/T} = \frac{-\sum_k A_k(\Delta H^0_{1,k-1} + \Delta H_k^\ddagger)/R}{\sum_k A_k}. \tag{79}$$

There are several points to be noted. If the overall irreversibility results from any w_j being *large* then all A_k with $k \geq j$ vanish from (79) and (77), if it results from any w_{-j} being *small* then all A_k with $k \geq j+1$ vanish. If a given w_j is *small* then all A_k with $k < j$ will be negligible. These are conditions on the w's and not on the rate constants; they may be met by the proper magnitude of the rate constant *or* concentration term involved. If a given k_i is small then the A_k with $k \geq i$ will predominate; the value of $\Delta H_i^\ddagger$ *may* be large relative to all others but the products $A_k\ \Delta H_k^\ddagger$ with $k > i$ are certainly not negligible relative to $A_i\ \Delta H_i^\ddagger$. Further it is not always lawful to assume that a large k_i implies a small $\Delta H_i^\ddagger$ or the converse for there are known cases of relatively rapid rates associated with strikingly large $\Delta H^\ddagger$ (Glasstone et al, 1941); the apparent discrepancy being accounted for by the entropy of activation $\Delta S^\ddagger$ which occurs in $\Delta F^\ddagger$ (cf. footnote p. 74). Finally it must be remembered that the $\Delta H^0_{1,j-1}$ from (74) are not independent of the $\Delta H_k^\ddagger$ since

$$\Delta H_k^0 = \Delta H_k^\ddagger - \Delta H_{-k}^\ddagger. \tag{80}$$

It is clear from the above and from the discussion in I that there are many ways of achieving overall irreversibility and conditions of "limiting rates": 1) If some w_j is *large*, then as discussed in I, if $j \neq 1$, the expression v_s reduces to that for the first $j-1$ steps. 2) If some w_{-j} is *small*, then the expression v_s reduces to that for the first j steps. These statements are general so long as the w in question is large or small because the corresponding rate constant is large or small. If w_j is large because $[C_j]$ is large, 1) is true only if C_j binds no catalytic component; otherwise the theorem of I applies;

viz., 3) the expression v_s reduces to that for the steps $j + 1$ through $j + r$, where the catalyst is returned to the free state in the $(j + r)$th step, and in this expression the concentration of bound catalyst is set equal to that of total catalyst. 4) If $w_{-n} = 0$ so that the overall process is irreversible, and w_j is *small,* it can be shown directly from (3) of I that

$$v_s = \left(\prod_{k=1}^{j-1} \frac{w_k}{w_{-k}} \right) G_{j,n}, \tag{81}$$

where $G_{j,n}$ is as defined in I. 5) If w_{-j} is *very small* and w_j is also *small,* so that the jth step is slow and irreversible, then from (66) or from (3) of I,

$$v_s = \left(\prod_{k=1}^{j-1} \frac{w_k}{w_{-k}} \right) w_j = \frac{1}{A_j}, \tag{82}$$

which is valid whether or not $w_{-n} = 0$.

It should be obvious that, mathematically and hence physically, all of the above cases are not quite independent. The above classification is best for purposes of clarity and convenience.

Setting aside, for the moment, the rather special case 5), it may be stated that *in general* in the above cases the rate expression has not reduced to that of a single limiting step. For example, in the case of the slow jth step, case 4) expressed by (81), the overall *rate* is indeed that of this step, it is in fact equal to the rate of any other step so long as steady state conditions are maintained; however, the rate *expression* has not reduced to that of a single step. Accordingly, in the above situations, $ln\ v_s$ vs. $1/T$ need not give a simple Arrhenius plot and if it appears to do so (and the following statement *includes* 5)) the T-dependence is still not governed by a single $\Delta H^\ddagger$ characteristic of a particular step. The rate expression *does* reduce to that for a single step in these cases, derivable from those above: a) If w_j is large and $j = 2$ the first $j - 1$ steps amount to just the first step. b) If w_{-j} is small and $j = 1$ the rate expression for the first j steps is again that for the first step alone. c) If $[C_j]$ is large and C_j binds a catalyst which is regenerated in the $(j + 1)$st step, i.e., $r = 0$ in statement 3) above, the rate expression is that for the $(j + 1)$st step. d) If the slow, irreversible step is the first one this is a degenerate case of (82) which gives $v_s = w_1$, the same result as b) above. The situation may now be summed up: In the general case the T-dependence of v_s is given by (77). The characteristics of the $ln\ v_s$ vs. $1/T$ curve is a problem for further work for the denominators of both terms in (77) are strongly T-dependent. For the case

4), expressed by (81), $\partial \ln v_s/\partial 1/T$ will be similar to (77) since the derivative of the first factor in (81) will produce $\Delta H^\circ_{1,j-1}$ and $G_{j,n}$ is of the same *form* as (66). For the case 5) it is evident by inspection from (82) and (76) that

$$\frac{\partial \ln v_s}{\partial 1/T} = -(\Delta H^\circ_{1,j-1} + \Delta H_j^\ddagger)/R. \tag{83}$$

Cases a) through d) require little discussion: When the conditions of these cases are met v_s reduces to the rate expression for a single step and the T-dependence of v_s is governed by the $\Delta H^\ddagger$ of this particular step, provided the concentration terms are temperature independent (see discussion to follow).

The physical interpretation of (81), (82) and (83) is simple to discover: $G_{j,n}$ in (81) is, according to (7) of I, the function which multiplied by $[X^s_{j-1}]$ gives v_s; the factor multiplying $G_{j,n}$ in (81) is, by (5) of I, the equilibrium concentration of X_{j-1}. Equation (81) then gives v_s as the rate of steps j through n when X_{j-1} is supplied to jth step at its equilibrium concentration. Equation (82) similarly gives v_s as the rate of steps j through n when X_{j-1} is at its equilibrium concentration, but under the conditions in 5), this reduces to the rate expression for the jth step, by 2) above, and w_j appears instead of a general term such as $G_{j,n}$. Actually then, (82) is the rate expression for the slow, irreversible jth step, but for reasons immediately to become obvious has been kept separate from a)—d).

It is a point of some importance that in the situation 5), expressed by (82) and (83), the plot of $\ln v_s$ vs. $1/T$ will be, to the extent that $\Delta H^\circ_{1,j-1}$ and $\Delta H_j^\ddagger$ are temperature independent, a straight line. In some quarters, as already mentioned, the slope of this line would be interpreted as a measure of $\Delta H_j^\ddagger$. The error so committed is clear from (83); the slope is determined not by $\Delta H_j^\ddagger$ alone but by $\Delta H_j^\ddagger$ plus the sum of all the standard heats of reaction, ΔH_k°, from 1 through $j - 1$. The physical situation is obvious: The condition for a "limiting step" has been met, in fact the rate of the slow, irreversible step is such that all preceding steps are essentially at equilibrium and the overall rate, (82), as already discussed, is just that of the slow step but this is not sufficient for the T-dependence of v_s to be governed by $\Delta H_j^\ddagger$ alone, for the equilibrium concentration of X_{j-1} is plainly temperature dependent. This is but an aspect of a more general problem already mentioned. When the rate of an overall process is given by the expression for the rate of a single-step irreversible process the expression is the product of a rate constant and one or more concentration terms. These concentration terms may themselves be temperature dependent: This may result from the temperature dependent distribution of any reactant or catalyst among active and inactive forms or among forms of varying activity; this includes inhibitions of *all* kinds. From results given in I, discussion p. 47, it follows that such distributions may be regarded as *equilibria,* though the main sequence of reactions are in the *steady state.* Although this had not previously been demonstrated, the assumption of equilibrium for such distributions has been the usual one in the past (Morales, 1947 and references therein, references in I). The T-dependence of such concentration terms thus enters through the equilibrium constants which describe the distributions mentioned above. More important, and this feature threatens the validity of many interpretations of "limiting steps and temperature coefficients" in *in vivo* systems, in open systems, *every* concentration is temperature dependent. Each concentration in the system is maintained by outside or environmental "sources" and "sinks." The temperature dependence in these cases is complex and enters through the diffusion factors of the environment and the system, permeability factors and the rate of the overall process in question (cf. examples in II and the many examples in Rashevsky, 1948).

The situation treated by M. F. Morales (1947) is a special case of c) above, the speciality resulting from the fact that in his case the compound which binds the catalyst is X_{j-1} and in order that $[X_{j-1}]$ be large it is necessary, in our terms, that R_n be small. His case may also be viewed as a special case of (82) wherein the expression for the equilibrium value of $[X_{j-1}]$ is obtained by solving the appropriate mass-action problem subject to the constraint of the material balance on the catalyst, equation (4) of I, and the condition that R_n be small. Morales carried the problem further than we have here indicated by considering the *effective* total concentration to be T-dependent by virtue of reversible denaturation. It should be noted that if the step in which the catalyst is regenerated is neither slow nor irreversible, statement c) still holds; in fact two such instances, equation (22) of I and discussion p. 39 of I, have already been given.

Once again we invite attention to the fact that by and large the "limiting conditions" discussed above can be met, in general, by concentration arrangement, without restricting the magnitude of rate constants which are inherent properties of the system. With this goes the important, if unfortunate, fact that in dealing with *in vivo* systems such arrangements are rarely possible. In the strict biological context the concentrations involved are, for a normal system under normal environmental conditions, be they internal and/or external, as much an innate property of the system as are the rate constants. Finally, if one could always deal with the T-dependence of rate constants most of the problems discussed above vanish. In general however the biologist must deal with *rates,* and these under the conditions existing in the system.

Some General Remarks.

There are many qualitative concepts which can be discussed in terms of the formulation given here. A number of these have been introduced by A. C. Burton (1939). For example Burton speaks of the "cost of transition" between steady states. In terms of "heat" this quantity has already been indicated in (60), or, in terms of free energy, and this seems more appropriate to "cost," in (47). Similarly the quantity $\boldsymbol{F}_s$ may be regarded as the "cost of maintenance," it is the free energy expenditure per unit time associated with the steady state and will be indicated in IV following, to be the rate of dissipation in the system. Burton further points out that the heat capacity of a steady state system may be expected to involve the "heats" associated with the temperature-induced concentration changes. This is of course true but is not a unique property of the steady state for such results are well known for equilibrium systems (Zemansky, 1943 p. 351). The computation is easily indicated for the system discussed in this paper, for

$$dH = \sum_k n_k \, d\widetilde{H}_k + \sum_k \widetilde{H}_k \, dn_k, \tag{84}$$

where the mole numbers n_k have been defined and the $\widetilde{H}_k$ are the partial molal enthalpies: If the variation (84) is due to a temperature change dT and, see discussion following (20), the changes in the mole numbers of the C_i and B_i are neglected and only the $[X_i{}^s]$ considered to change, (84) yields

$$\left(\frac{\partial H}{\partial T}\right)_P \equiv C_P = \sum_k n_k \widetilde{C}_{Pk} + V \sum_k \widetilde{H}_{x_k} \left(\frac{\partial [X_k{}^s]}{\partial T}\right)_P . \tag{85}$$

The first summation, in which $\widetilde{C}_{Pk}$ are the partial molal heat capacities, is the heat capacity of the system as if it were an inert mixture, the last summation is the contribution due to the change in the X-concentration: The $\partial[X_k{}^s]/\partial T$ are readily obtained from (5) of I written as

$$[X_k{}^s] = \frac{K_{1,k}}{R_k} - v_s / V_{-i,1} \, , \tag{86}$$

where $V_{-i,1}$ is defined in I, and using (68) and (69) of this paper. It is not worthwhile to carry this out here.

There has appeared in this paper no quantity which corresponds to what Burton calls the "potential energy." The "potential energy" for an equilibrium system is the thermodynamic potential or F, which is a minimum at equilibrium: If such a system be displaced from equilibrium and abandoned, F will decrease until the minimum value again obtains. If a steady state system be displaced it will also return, so far as the $[X_k^s]$ are concerned to the original condition; the system discussed here does not return to its original F-value; the difference between the F-flux at any stage of the recovery and that in the steady state, (26), has been discussed but the difference in the F-values has no real meaning in the sense that it does for an equilibrium system. It is a fundamental problem to inquire whether there exists for a steady state system a function which has the property (which the various thermodynamic functions have for an equilibrium system) that it is a maximum or minimum in the steady state. This question, to the author's knowledge, first raised by A. J. Lotka (1925 p. 321) has been discussed in interesting and definite terms by F. Zwicky (1933). The specification of a steady state system is a different problem from the specification of an equilibrium system in that, for an n-step system, $2n$ w's must be prescribed; this involves $2n$ rate constants and as many concentration terms as are included in the w's. The condition for the steady state is, (23), $v_k = v_{k+1}$ for all k and there are elaborate tests (Lotka, 1925; Garder and Barnes, 1942 and refs. therein) for the stability of the steady state but it remains a problem to relate these conditions to any energetic criteria.

We have discussed only "straight-chain" sequences of reactions in this paper. The extension of these formulations to the branched or coupled systems treated in I offers no difficulty, for example $\boldsymbol{F}(t)$ is still given by summing $\Delta F_i \, v_i$ over all steps, cf. (8), (16). In connection with this type system and closely related to the conclusion from (21) and (22) is the following problem: Consider a system in which a substrate is being oxidized with the concomitant formation of an "energy-rich" compound and which is at least triply branched and coupled in that 1) the reduced coenzyme is reoxidized via a hydrogen transport chain, cf. I; the energy rich compound donates a group, usually a high-energy phosphate, to an acceptor; 2) the organic moiety, divested of the donated group, suffers some further fate via a chain of reactions and 3) the now energy rich acceptor, X, can possibly divest itself of the accepted group via one or more pathways which may include wasteful splitting or spontaneous decomposition. Now the steady state (*or* time dependent) concentration of X is determined by the *rates* of all of these processes. A given process which requires or must be "driven by" X will not take place unless the concentration of X is sufficiently great; in fact this process will, according to (22), run backwards. Thus if the rate of utilization of the substrate is not sufficiently rapid the oxidative process cannot "drive" the process in question; specifically the rates of the primary dehydrogenation and process 2) above must be rapid, meaning that, in the steady state, the forward w's of these steps must be great. The situation is simply that the *concentration* of X is determined by the *rates* involved and that free energy, residing in the substrate and ultimately available in the form of energy-rich acceptor may be sufficient to "drive" the process in question; this does not occur if the chemical potential, given in its dependency on concentration by (2), does not become sufficiently great. The acceptor is not necessary to the above picture and frequently the energy-rich compound, such as an acyl-phosphate, *per se* participates in synthesis etc.; the general argument remains the same. On the above basis a given synthesis, dependent upon an oxidative process, will not occur unless rate of the oxidative process is sufficient, in fact by (22), degradation will occur. Further there will be competition, for "energy," in that rapid syntheses keep the X-concentration at a level insufficient for some slower processes to occur. Likewise there will be competition between "maintenance" and function, to the extent (which is not known) that function depends upon the concentrations of energy-rich intermediates in the same way as do rate processes; there may also be competition between any metabolically supported processes subserved by the same group of energy rich intermediates. It is a simple problem to verify the above statements in principle. Their experimental importance is, of course, another question; a complete discussion cannot be given here. A presumptive case of the failure of an oxidative process to support function due to insufficient rate is known (Tschirgi et al, 1949). An example of competition between syntheses is that between the syntheses of virus and normal protein. It would be interesting to investigate the energetics of development (Tyler, 1942) and similar processes from the above point of view.

It will be mentioned here that the formulations in this paper are clearly applications of classical thermodynamics to systems in which changes, irreversible and of any rapidity, are occurring. It may seem unnecessary to make such a remark at all, but the idea is sufficiently prevalent that the methods of thermodynamics are not available for non-equilibrium systems and irreversible processes and the failure to recognize thermodynamic methods in unfamiliar context sufficiently frequent that this will be discussed at the close of IV following.

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THE STEADY STATE KINETICS OF SOME BIOLOGICAL SYSTEMS: IV. THERMODYNAMIC ASPECTS

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The investigation initiated in III is continued. The irreversible production of entropy and the rates of dissipation in diffusion fields and due to chemical reactions are discussed. The rates of change of free energy, entropy, etc. are indicated for type-systems of biological interest in which composition and reaction rates are a function of position. Some consequences of Onsager's generalization of Fick's Law are discussed in terms of maintenance of stationary, non-equilibrium concentration distributions, transport of a solute against a concentration gradient, and the dependence of these phenomena upon metabolism.

In the introduction of part III (Hearon, 1950) it was indicated that the dissipative or irreversible aspects of processes are of some general interest for the reasons there stated and frequent reference was made to "dissipation" in steady state systems. It was further proposed there to discuss, in this part, open systems and systems in which space gradients of the thermodynamic quantities occur. We begin here by discussing the irreversible production of entropy.

1. *The Irreversible Entropy and Dissipation.*

In *principle* there will be nothing new in this section: There are, as has been indicated in III, many excellent treatments of what is essentially this same topic. Th. De Donder first introduced explicitly the "uncompensated heat" of a process (1936 and references therein). He did not employ the term *irreversible entropy* but related the uncompensated heat to what he termed the *affinity* (see also Van Rysselberghe, 1935). The affinity is shown to be

$$\begin{aligned} Affinity &\equiv \frac{d\,q^*}{d\,\xi} \\ &= -\left(\frac{\partial F}{\partial \xi}\right)_{P,T} = -\sum_k \nu_k \,\mu_k, \end{aligned} \tag{1}$$

where q^* is the uncompensated heat, ξ is the extent of the reaction and the members of the second equality have been defined and discussed in III [equation (5)]. The development leading to the result (1), while an essential part of the logical apparatus in the remarkable De Donder-Van Rysselberghe exposition of thermodynamics, is not very direct. Furthermore the formulations of these authors are restricted to systems the composition of which can be specified by one or more variables ξ_j; in particular they are not readily adapted to processes such as diffusion. In a general treatment of irreversible processes L. Onsager (1931a, b, 1932) constructs for transport processes, notably diffusion (see also Harned, 1947), a *dissipation-function*: Twice the dissipation-function gives the time rate of change of the irreversible entropy. In Onsager's treatment there is no necessity for the distinction, which will be made in what follows, between total and irreversible entropy.

In the general treatment of irreversible processes by C. Eckart (1940a, b) the separation of the irreversible entropy change from the total entropy change is actually made but not quite in these terms. It is perhaps permissible to state here that Eckart's very general object (1940b) was to inquire for the restrictions imposed by the second law of thermodynamics upon the equations, which he calls the thermodynamic equations of motion (cf. Onsager, 1931a, b), which describe irreversible processes† and to derive equations of the form [Eckart's equation (1) in the notation of this paper],

$$\frac{d}{dt}\int_V S\,dV + \int_\sigma (\vec{q}/T)\cdot d\vec{\sigma} = \int_V G\,dV\,, \tag{2}$$

which, with the constraints of the second law of thermodynamics, give

$$G \geq 0\,, \tag{3}$$

where S is the total entropy per unit volume, $\vec{q}$ the vector of heat flow and $d\vec{\sigma}$ the vector element of surface with direction of the outward normal. The quantity G in (2) and (3), given explicitly in Eckart's equation (26), may be identified at once with what we, following R. C. Tolman and P. C. Fine (1948), will call the (time) rate of irreversible production of entropy per unit volume. J. Meixner (1941, 1942, 1943) and B. Leaf (1946) have presented treatments similar to that of Eckart (1940b). Both of these workers use the term *dissipation* in the sense that we will immediately employ it.

In view of all of this it merits some comment that what we hope to achieve in this section and in the remainder of this paper is some sort of synthesis of the above-mentioned results in a fairly direct, if simple, treatment. This will be carried out in a manner strongly directed toward our interests here, which are not too general, and with regard for rendering complete certain statements and formulations in III. More especially there will be discussed and employed a simple expression for the irreversible production of entropy which applies to a large class of processes. It includes, for example, many of the individual cases treated by Tolman and Fine (1948). It should be made clear that generality was no primary concern in their work the burden of which was to compute from the familiar integral $\Delta S = \int dq/T$, taken over a *reversible* path, the irreversible production of entropy for a host of individual cases, to provide a logically satisfactory basis for this procedure and to examine the rigor with which the *rate* of irreversible production of entropy can be computed.

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†We have already referred, in III, to his conclusion that these restrictions are fulfilled by the formal kinetic rate equations for chemical reaction.

Since most of the above cited investigators have made little reference to previous and related work, the relations which are *briefly* and incidentally pointed out in what follows may be helpful outside of the immediate context of III and of this paper.

Although the total entropy, S, is an extensive quantity and is in this sense an additive property (see Epstein, 1937 for a careful statement) it is, according to the second law of thermodynamics, not a quantity which is conserved in irreversible processes. Thus in considering the total entropy change of a system it is necessary to account for the entropy reversibly communicated to the system across the boundary and the entropy *produced* within the system. Denote by S_r the reversibly transported entropy and by S^* the entropy generated within the system by irreversible processes. The total entropy change is then (cf. La Mer et al, 1949)

$$dS = dS_r + dS^*. \tag{4}$$

Let dq be the thermal energy received by the system in *any* variation. Let dq^* be the heat irreversibly evolved within the system: this is the uncompensated heat already mentioned. The second law states that

$$T\,dS \geq dq\,. \tag{5}$$

The *equality* statement of the second law (De Donder, 1936) is that

$$T\,dS = dq + dq^*. \tag{6}$$

From (5) and (6) we get

$$dq^* \geq 0\,. \tag{7}$$

For a reversible process the equality in (5) and (7) holds. If no matter is transported into the system and entropy is carried into the system by heat transfers alone, then we find

$$\left.\begin{aligned} dS_r &= dq/T\,; \\ dS^* &= dq^*/T\,. \end{aligned}\right\} \qquad (8)$$

The last equation in (8) obtains whether or not matter is exchanged with the environment. If the quantities in the last equation of (8) be referred to a unit volume of system and the time derivatives formed from the differentials there is obtained Eckart's quantity G [equation (1)]. The inequality (7), demanded by the conventional second law (5), is equivalent to (2).

It should be mentioned here that we have (1949a, b, referred to as I and II), in purely kinetic discussions and in III, freely used the term *irreversible* to describe a reaction in which the reverse or backward rates can be neglected: This is not to be confused with *thermodynamic irreversibility,* here discussed, to which it bears little relation for all reactions under non-equilibrium conditions are thermodynamically irreversible. We will also assume as true the corollary of the second law that processes which are proceeding at a finite rate are irreversible but note in passing the hypothetical exceptions discussed by J. Meixner (1942) and the relativistic situations discussed by R. C. Tolman (1934, p.134, 319). These exceptions need not concern us here.

Now the method of computing dS^* or, for a finite change, ΔS^* will naturally be determined to a large extent by the system and processes in question. In general ΔS^* will consist of terms giving the contribution from diffusion, spontaneous chemical reaction, mixing, heat flow, work against viscous forces, etc. As has been shown (Tolman and Fine, 1948) the calculation of these terms can usually be made by computing $\int dq/T$ over a reversible path connecting the initial and final states of the system. One has only to invent a process entailing the reversible absorption of heat which will produce the same change in the system as that produced by the irreversible process in question: The limitations imposed on the use of this method have been carefully discussed (Tolman and Fine, 1948). In the case of thermal effects alone this procedure is simple. For other processes greater resource is required on the part of the computer to conceive of a process involving reversible heat exchange which will produce the desired effect. The following method is most frequently available; in particular it is of use for the processes of diffusion and chemical reaction in which we are chiefly interested.

Consider a system, in which any process is occurring, to be placed in thermal contact with a huge, infinite, if necessary, heat reservoir. The temperature, T, of the system and reservoir will be the same and the combination, system plus reservoir, will operate at constant energy E and constant volume V. It is clear that if the change in entropy be computed for the combination, taking account of the fact that the reservoir can lose energy and volume to the system, the entropy change so computed will be just the irreversible production of entropy in the system. Consider the entropy of the system, $S_a(T, P, x_i)$, to be a function of the temperature, pressure and any number of parameters, x_i, which specify the composition. Consider the entropy, $S_b(E_b, V_b)$, of the reservoir to be a function of the volume and energy. We exclude for the moment exchange of matter between the system and reservoir. A change in the parameters x_i produces a change,

$$dS_a = \sum_i \frac{\partial S_a}{\partial x_i} dx_i, \tag{9}$$

in the entropy of the system and changes,

$$\left.\begin{aligned} dE_a &= \sum_i \frac{\partial E_a}{\partial x_i} dx_i, \\ dV_a &= \sum_i \frac{\partial V_a}{\partial x_i} dx_i, \end{aligned}\right\} \tag{10}$$

in the energy and volume. Because of the constancy of total energy, $E = E_a + E_b$, and volume, $V = V_a + V_b$, the changes (10) cause equal and opposite changes in the reservoir,

$$\begin{aligned} dE_b &= -dE_a, \\ dV_b &= -dV_a \end{aligned} \tag{11}$$

with the result that the entropy of the reservoir changes by the amount,

$$\begin{aligned} dS_b &= \frac{\partial S_b}{\partial E_b} dE_b + \frac{\partial S_b}{\partial V_b} dV_b \\ &= \frac{1}{T} dE_b + \frac{P}{T} dV_b. \end{aligned} \tag{12}$$

For the total entropy change, $dS_a + dS_b$, there is obtained, by using (10) and (11) in (12) and adding the result to (9),

$$(dS)_{E,V}=\sum_i \frac{\partial S_a}{\partial x_i}\,dx_i-\frac{1}{T}\sum\frac{\partial E_a}{\partial x_i}\,dx_i-\frac{P}{T}\sum_i\frac{\partial V_a}{\partial x_i}\,dx_i. \tag{13}$$

But at constant T and P,

$$dS_a-(dE_a+PdV_a)/T=-\frac{dF_a}{T} \tag{14}$$

and (13) gives

$$(dS)_{E,V}=-\frac{(dF_a)_{T,P}}{T}=dS^*. \tag{15}$$

The above is in all essentials the same as the method employed by J. Mayer and M. G. Mayer (1940) to show from the second law statement, $(dS)_{E,V}\geq 0$, that F must decrease in spontaneous processes. In the above derivation it was assumed that T and P were uniform throughout the system. The composition was not assumed uniform and the irreversible processes taking place in the system might include mixing, redistribution of concentration gradients with transport from regions of higher to regions of lower chemical potential, etc.†

Consider now the situation that the reservoir contains all of the chemical species contained in the system and that exchange of matter may take place between the system and reservoir. Let S_a, E_a and V_a be functions of T, P and the mole numbers n_{ia} and S_b be a function of E_b, V_b and n_{ib}. In place of (9) we now have

$$dS_a=\sum_i \tilde{S}_{ia}\,d\,n_{ia}, \tag{16}$$

where the $\tilde{S}_{ia}$ are the partial molal entropies in the system and (12) is replaced by

$$dS_b=\frac{1}{T}\,dE_b+\frac{P}{T}\,dV_b-\frac{1}{T}\sum_i \mu_{ib}\,d\,n_{ib}, \tag{17}$$

where the μ_{ib} are the chemical potentials in the reservoir:

$$\left(\frac{\partial S_b}{\partial n_{ib}}\right)_{E_b,V_b}=-\mu_{ib}/T. \tag{18}$$

From (17), (11) and (16) there results

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†It may then be true that (9) and (10) may not be expressible by a finite number of x_i and a space integral may be necessary but only the changes dS_a, dE_a and dV_a, *whatever* their form, appear in (13) and the argument holds.

$$
\begin{aligned}
(dS)_{E,V} &= dS_a - \frac{1}{T}\,dE_a - \frac{P}{T}\,dV_a - \sum_i \frac{\mu_{ib}}{T}\,dn_{ib} \\
&= -\frac{(dF_a + dF_b)_{T,P}}{T}.
\end{aligned}
\tag{19}
$$

Since in (19), dS_a is given by (16) and dE_a and dV_a by

$$dE_a = \sum_i \tilde{E}_{ia}\,dn_{ia} \tag{20}$$

and

$$dV_a = \sum_i \tilde{V}_{ia}\,dn_{ia}, \tag{21}$$

where $\tilde{E}_{ia}$ and $\tilde{V}_{ia}$ are the partial molal energies and volumes, and the relations,

$$
\begin{aligned}
\mu_{ia} &= \tilde{H}_{ia} - T\,\tilde{S}_{ia}, \\
\tilde{H}_{ia} &= \tilde{E}_{ia} + P\,\tilde{V}_{ia}
\end{aligned}
\tag{22}
$$

obtain among the partial molal quantities in question, it is readily seen that the contribution to $dF_a + dF_b$ due to transport of matter from the reservoir to the system will vanish if $\mu_{ia} = \mu_{ib}$ for all i. Thus if the chemical potentials are equal in the system and reservoir equation (19) still gives the change due to spontaneous processes in the system. If the composition of the *system* is not uniform, (16) must be computed by considering the dn_{ia} to be the change in the mole numbers for a unit volume and integrating over the volume of the system. The point of importance is that if the surface values of μ_{ia} and μ_{ib} are equal, (19) still gives the change due to irreversible processes in the system since that due to transport across the surface will vanish as discussed above and (19) gives the change due to transport, *in the system,* along gradients of chemical potential, chemical reaction, etc. This case of the reservoir containing matter which can be exchanged with the system has been discussed because of the strict formal analogy, which later becomes clear, to the cell imbedded in an infinite medium:

From (15) and from the familiar

$$\Delta F = \Delta H - T\,\Delta S, \tag{23}$$

which holds at constant T, it is seen that ΔS and ΔS^* are identical if $\Delta H = 0$, i.e. for a process for which the enthalpy change is zero the total entropy change and the irreversible production of entropy are the same. This is in fact the case for the mixing of isotopes or of perfect gases, for in these processes

$$\Delta S = -\Delta F/T \tag{24}$$

(Mayer and Mayer, 1940). This will be shown in the next section to be the case also for diffusion in perfect, dilute solutions. Using (4) in (23) gives

$$\Delta F = \Delta H - T(\Delta S_r + \Delta S^*), \tag{25}$$

and comparison to (15) suggests that

$$\Delta H = T \Delta S_r . \tag{26}$$

It may be argued that at constant T, when (23) and (25) apply, the heat ΔH is absorbed by the system from the environment reversibly. That this fact is included in (15) may be easily shown in a manner which will exhibit the T-dependence of ΔS^*. Differentiation of both sides of

$$-T \Delta S^* = \Delta F \tag{27}$$

with respect to T and using the relation

$$\frac{\partial \Delta F}{\partial T} = -\Delta S = -(\Delta S_r + \Delta S^*) \tag{28}$$

show that

$$\frac{\partial \Delta S^*}{\partial T} = \Delta S_r/T . \tag{29}$$

But also

$$\frac{\partial \Delta S^*}{\partial T} = -\frac{\partial \Delta F/T}{\partial T} = \Delta H/T^2 . \tag{30}$$

Comparison of (29) and (30) gives (26).

The quantity TdS^*, or $T \Delta S^*$, gives, cf. (8), the uncompensated heat and represents the amount of dissipation associated with the process in that this amount of energy, formerly available for useful work, has become completely unavailable for work at *the temperature* T *in question* [cf. discussion by Zemansky, 1943, p. 167 wherein the amount of energy which becomes unavailabe is $T_0 \Delta S$(system) + $T_0 \Delta S$(environment), where T_0 is the temperature of the coldest available heat sink]. This is easily seen (LaMer et al, 1949) by substituting dq from (6) into the first law of thermodynamics (see also Tolman and Fine, 1949). Thus $T\left(\frac{dS^*}{dt}\right)$ gives the rate of dissipation:

this is a form of Kelvin's principle of degradation of energy.

2. *Free Energy Change and Dissipation in Diffusion.*

Consider the diffusion of a solute from a point where the chemical potential is $\mu(1)$ to a point where the chemical potential is $\mu(2)$. For one mole the change in free energy is $\mu(2) - \mu(1)$ and using (15) in the form of (27)

$$T \Delta S^* = -\{\mu(2) - \mu(1)\}. \qquad (31)$$

Taking μ to be of the form [(2) of III]

$$\mu = \mu^0 + R\,T \ln C \qquad (32)$$

gives

$$T \Delta S^* = -R\,T \ln \frac{C(2)}{C(1)}. \qquad (33)$$

Since μ is related to the partial molal enthalpy $\tilde{H}$ by

$$\frac{\partial \mu/T}{\partial T} = \frac{\partial \mu^0/T}{\partial T} = -\tilde{H}/T^2 \qquad (34)$$

and μ^0 is independent of concentration (cf. III), it is implicit in (32) that the transfer of solute from one concentration to another is not accompanied by the absorption of heat. Thus ΔS^* in (33) is identical with ΔS.

Consider an infinitesimal cube located at the general position x, y, z. The rate of transport across the face in the y-z plane in the positive x-direction is $J_x\,dydz$, (Moles/time), where J_x is the x-component of the diffusion current $\vec{J}$. The change in free energy, for one mole, in being transported the distance dx is $\frac{\partial \mu}{\partial x}\,dx$. Thus the time rate of change of free energy per unit volume, when there is no accumulation in the volume $dx\,dy\,dz$, due to flow in the positive x-direction, is $J_x \frac{\partial \mu}{\mu x}$. Adding the similar terms for flow in the y and z directions gives for the time rate of change of free energy per unit volume

$$\frac{dF}{dt} = \nabla \mu \cdot \vec{J}, \qquad (35)$$

where F is the free energy per unit volume. Thus the total rate of change due to diffusion is

$$\frac{dF}{dt} = \int_V \nabla \mu \cdot \vec{J}\, dV, \tag{36}$$

where F is the total free energy. From (15) and (36) there is obtained

$$T\frac{dS^*}{dt} = -\int_V \nabla \mu \cdot \vec{J}\, dV \tag{37}$$

as the total rate of dissipation due to diffusion. It can easily be shown that (37) gives the work per unit time against frictional forces. Let $\vec{J}$ be given by the simple Fick's Law

$$\vec{v}\,C = \vec{J} = -D \nabla C. \tag{38}$$

The velocity of diffusion is

$$\vec{v} = -D \nabla C/C = -\frac{D}{RT} \nabla \mu. \tag{39}$$

Now one may, following E. A. Guggenheim (1929), regard $\nabla \mu$ as the force on a mole of solute (cf. Hartley, 1931; Harned, 1947) and identify RT/D as the "frictional coefficient." The work per unit time, per mole against frictional resistance is then

$$-\nabla \mu \cdot \vec{v} = -\nabla \mu \cdot \vec{J}/C. \tag{40}$$

Since there are C moles per unit volume the work per unit time per unit volume is

$$-\nabla \mu \cdot \vec{v}\,C = -\nabla \mu \cdot \vec{J}. \tag{41}$$

Integration of (41) over the volume in question gives (37). N. Rashevsky (1943) has derived (41) in the form $DRT(\nabla C)^2/C$ without use of the chemical potential but by invoking the Stoke's Law expression for the force of resistance upon a spherical particle. The result (37) holds whatever the form of $\vec{J}$ so long as this is the current of *diffusion.* Thus $\vec{J}$ need not be given by (38), which was used only to show that (37) also represented degradation of energy by friction, but may be taken from Onsager's (1932, 1945) generalization of Fick's Law which we will later mention and use. The current $\vec{J}$ however must not include a convection term for then the change in free energy would include a term due to transport into the region which does not represent dissipation. When convection does occur (37) may be derived by considering an infinitesimal cube which moves with the fluid and the volume V of integration in (37) would likewise be considered to move with the fluid.

3. *Free Energy Change and Dissipation for Chemical Reaction.*

With the aid of (15) and the formulations of III this topic may now be disposed of rather simply. From (15)

$$\frac{dS^*}{dt} = -\frac{1}{T}\frac{dF}{dt} \tag{42}$$

and $\frac{dF}{dt}$ is in general to be taken from equation (8) or (14) of III or, if the steady state obtains, from equation (16), (20) or (43) of III. The total rate of dissipation, $T\left(\frac{dS^*}{dt}\right)$, due to chemical reaction is $-\frac{dF}{dt}$ from equations (8), (4), (16), (20) or (43) of III. Similarly equation (26) of III gives the difference between total rates of dissipation in the time dependent and steady states. Equations (44), (45) and (46) of III give the difference between the rates of dissipation in two steady states when the transition between steady states has been induced by one of the various means discussed in III. Equations (51) and (52) of III, with a change in sign, give the T-dependence of the rate of irreversible production of entropy and the rate of dissipation respectively. The rate of dissipation $T\left(\frac{dS^*}{dt}\right)$ is required by the second law, equations (7) and (8), to be positive. By writing (42) in either of the forms in the notation of III

$$\begin{gathered} T\frac{dS^*}{dt} = -\boldsymbol{F}; \\ T\left(\frac{dS^*}{dt}\right)_s = -\boldsymbol{F}_s, \end{gathered} \tag{43}$$

where the second form holds for the steady state, and recalling that in III it has been shown that $\boldsymbol{F} \leq 0$, $\boldsymbol{F}_s \leq 0$, one obtains from a slightly different approach confirmation of the fact, cf. discussion p. 63–65 of III, that the rate laws of formal kinetics are in accord with general thermodynamic principles (cf. Eckart, 1940b).

It should be mentioned that LaMer et al (1949) have derived the equivalent of (42) for chemical reaction by employing their powerful and elegant *rule of potentials* (p. 618 LaMer et al, 1949) which cannot be discussed here but to which we wish to direct attention.

We return for the moment to the discussion of section 1 of this paper. Th. DeDonder (1936) gives dq^*/dt as

$$\frac{dq^*}{dt}=\frac{dq^*}{d\xi}\,\frac{d\xi}{dt}. \tag{44}$$

From (1), cf. (5) and (6) of III, this is $-\frac{dF}{dt}$. DeDonder defines dq^*/dt as the "power of the system" and shows that it must be positive: It is readily seen from the discussion in section 1 of this paper and in III that this is equivalent to our demonstration that $\boldsymbol{F} \leq 0$, $\boldsymbol{F}_s \leq 0$.

It is worthy of mention that the relation discussed above between dissipation and free energy change gives some insight into the much discussed (Lipman, 1941; Barron, 1943) situation that biological systems are usually characterized by processes which take place in many "nearly reversible" steps and which are thus less wasteful. Similarly the conservation of free energy resulting from the coupling of processes such as oxidation and phosphorylation (Lipman, 1941; cf. III) receives a somewhat clearer interpretation in terms of dissipation.

In order to extend the results of this section and those of III to systems in which the concentrations of the various components are functions of position we give the following discussion: Consider an element of volume ΔV sufficiently small that the concentration may be considered uniform within the element. Let $\bar{F}$ be the free energy and $\bar{n}_k$ the number of moles of the kth solute in the element. Then

$$\bar{F}=\sum_k \mu_k \bar{n}_k, \tag{45}$$

where the μ_k are uniform in the element. If the volume element approaches zero

$$\lim_{\Delta V\to 0}\frac{\bar{F}}{\Delta V}=F=\sum_k \mu_k C_k, \tag{46}$$

where F has already been defined as the free energy per unit volume and the concentration C_k is the number of moles per unit volume, at the point in question, of the kth solute. In a system with space distributions of concentration it is no longer true that the total free energy F is a homogeneous function of the mole numbers of degree one; for the number of moles of the kth solute is

$$n_k = \int_V C_k \, d\, V$$

and the total free energy is

$$F = \int_V F \, d\, V = \int_V \sum_k \mu_k \, C_k \, dV. \tag{47}$$

Similar statements apply to the other so-called extensive properties. The free energy per unit volume from (46) is clearly a homogeneous function, of degree one, of the C_k and the usual theorems based on this fact apply. In particular we have

$$\sum_k C_k \frac{\partial \mu_j}{\partial C_k} = \sum_k C_k \frac{\partial \mu_k}{\partial C_j} = 0, \tag{48}$$

and

$$\sum_k C_k \, d\, \mu_k = 0; \quad d\, T = d\, P = 0, \tag{49}$$

which are, for a unit volume of system, forms of the familiar Gibbs-Duhem rule (cf. Vegard, 1910). Thus from (46) and (49) the rate of change of free energy per unit volume, at constant T and P is

$$\frac{d\, F}{dt} = \sum_k \mu_k \frac{d\, C_k}{dt} \tag{50}$$

in which μ_k and C_k are evaluated at the point in question and dC_k/dt is *due solely to chemical reaction.* If dC_k/dt be evaluated in terms of the kinetic rate equations the result is obviously equation (8) or (14) of III with the factor V deleted. In fact it was indicated in III that $\Delta F_i v_i$ gives the rate of change of free energy *per unit volume* due to the ith step. The factor V appears in (8) of III because of this. If (50) so expressed be integrated over the volume of the system the total rate of change of free energy due to chemical reaction is obtained. If the steady state obtains (50) is given by equation (16), (20) or (43) of III with the factor V deleted.

4. *Metabolizing Systems.*

Consider a system in which any number of substances are being produced by chemical reactions at the rates, per unit volume, q_i which may or may not be independent. The equation of continuity is

$$-\nabla \cdot \vec{J}_k + q_k = \frac{\partial C_k}{\partial t}. \tag{51}$$

And the total rate of change of free energy is

$$\frac{dF}{dt}=\frac{d}{dt}\int_V F\,dV=\int_V \sum_k \mu_k \frac{\partial C_k}{\partial t}\,dV, \qquad (52)$$

where $\partial C_k/\partial t$ is due, by (51), to diffusion *and* reaction. Combining (51) and (52) and applying the divergence theorem gives

$$\frac{dF}{dt}=\int_V \sum_k \mu_k q_k+\int_V \sum_k \nabla\mu_k\cdot\vec{J}_k\,dV-\int_\sigma \sum_k \mu_k \vec{J}_k\cdot d\vec{\sigma}, \qquad (53)$$

where σ is the surface enclosing the volume V. Since $q_k < 0$ for consumption the first integral is a contribution from chemical reaction; the intergrand is given by (50) and may be expressed in terms of the formulae of III as discussed in section 3. The second integral is by (36) the contribution due to diffusion. The surface integral is the contribution due to influx of matter at the rate $\vec{J}_k\cdot d\vec{\sigma}$ moles per unit time through the element of area $d\sigma$, each mole of the kth solute bringing in free energy in the amount μ_k. It is clear that a similar procedure will give the rate of change of entropy when

$$\frac{dS}{dt}=\int_V \sum_k \tilde{S}_k \frac{\partial C_k}{\partial t} \qquad (54)$$

is used and so on for any thermodynamic quantity, for the argument leading to (46) may be applied to any quantity and the corresponding partial molal quantities.

What can be done to carry the problem further depends entirely upon the solutions of the set (51). As is well known, if the q_k are related by the fact that any q_k depends upon other concentrations C_j, even the steady state solutions of (51) are usually unavailable. When q_k is just proportional to C_k the steady state solutions are rather unwieldy (Rashevsky, 1948). When the $\vec{J}_k$ are not independent, as will be true when Onsager's generalized law (1945) is used, situation arise, to be mentioned later, not previously treated. There are a few points however which are worth discussing with the aid of very simple examples.

It is clear from (52) that when the steady state has been attained, $\dfrac{\partial C_k}{\partial t}=0$ for all k, $\dfrac{dF}{dt}$ is zero. The integrals in (53) extended over the volume of the cell, (system), and its boundary surface σ must cancel: the contributions from chemical reaction, diffusion along gradients of chemical potential and influx of matter must balance. When one considers the medium, for which the equation of continuity is

$$-\nabla\cdot\vec{J}=\frac{\partial C_k}{\partial t}, \tag{55}$$

in place of (53) there is

$$\left(\frac{dF}{dt}\right)_{\text{medium}}=\int_V\sum_k\nabla\mu_k\cdot\vec{J}_k\,d\,V-\int_\sigma\sum_k\mu_k\vec{J}_k\cdot d\,\vec{\sigma}. \tag{56}$$

Equation (56) must also vanish when the steady state obtains. Here we encounter a difficulty pointed up in III: If among the boundary conditions on (55) is the usual condition that $C_k\rightarrow C_k{}^0$ at infinity then it is considered that material is added to or withdrawn from the medium, by reactions in the cell, without changing the concentration distribution. Thus there results the situation that material flows into the cell, reacts, products flow out; all with no change in free energy. In the system discussed in III the free energy change accompanying the conversion of reactants to products was admitted but, in the rate equations, changes in concentration were not admitted. In the problem discussed here the situation is not so simple to remedy. The problems associated with the "infinite medium" were early discussed by N. Rashevsky (1948, preface to first edition).

Consider the simple case of a spherical cell of radius r_0 in which the reaction $C\leftrightarrows B$ occurs. Let there be no gradients except in the membrane. The rate of change of free energy for the cell *and* environment due to diffusion of a single solute is,

$$\left(\frac{dF}{dt}\right)_{\text{diff}}=-D_{km}\,R\,T\,4\,\pi\int_{r_0}^{r_0+\delta}\left(\frac{\partial C_k}{\partial r}\right)_m\frac{\partial\,ln\,C_k}{\partial r}\,r^2\,dr, \tag{57}$$

where $(\partial C_k/\partial r)_m$ is the gradient in the membrane which is assumed constant, D_{km} the diffusion coefficient in the membrane and δ the thickness of the membrane. Equation (57) gives approximately

$$\left(\frac{dF}{dt}\right)_{\text{diff}}=-D_{km}\,R\,T\left(\frac{\partial C_k}{\partial r}\right)_m 4\,\pi\,r^2\,ln\frac{C_k(r_0+\delta)}{C_k(r_0)}. \tag{58}$$

Since $C(r_0)$ and $C(r_0+\delta)$ correspond to C_0 and C_i, the external and internal concentrations, (58) gives

$$\left(\frac{dF}{dt}\right)_{\text{diff}}=-h_k\,A\,(C_0-C_i)\,R\,T\,ln\frac{C_0}{C_i}, \tag{59}$$

where $hA\,(C_0-C_i)$ is the familiar expression (Rashevsky, 1948) for the flow into the cell with h the permeability constant and A the area of the cell. Let the reaction be proceeding at the steady state rate

$v_s = k_1[C] - k_{-1}[B]$ and let $[C]_0$ and $[B]_0$ denote the external concentrations. Now, cf. III,

$$\left(\frac{dF}{dt}\right)_{\text{react.}} = V\left(\Delta F^0 + RT\,ln\,\frac{[B]}{[C]}\right) v_s \tag{60}$$

and

$$\begin{aligned}\left(\frac{dF}{dt}\right)_{\text{diff}} &= h_C A([C]_0 - [C])\,RT\,ln\,\frac{[C]}{[C]_0} \\ &\quad + h_B A([B] - [B]_0)\,RT\,ln\,\frac{[B]_0}{[B]}.\end{aligned} \tag{61}$$

In the steady state

$$Vv_s = h_C A([C]_0 - [C]) = h_B A([B] - [B]_0). \tag{62}$$

Thus the sum of (60) and (61) gives

$$\left(\frac{dF}{dt}\right)_{\text{total}} = V\left(\Delta F^0 + RT\,ln\,\frac{[B]_0}{[C]_0}\right) v_s, \tag{63}$$

where ΔF^0 is defined in III. Equation (63) gives the rate of change of free energy for the conversion of C to B *at the external concentrations* $[C]_0$ and $[B]_0$ at the rate v_s. The physical situation behind (63) is certainly clear. This simple example suggests at once that the method of avoiding the difficulties caused by the "infinite medium" (which is a necessity for solving the boundary value problems of diffusion in closed form) is to employ the approximation method of Rashevsky (1948). This will involve certain problems but, in general, one has only to set up approximate gradients and find approximate volumes to replace the volume integrals.

Thus far we have wherever possible left the form of the diffusion currents $\vec{J}_k$ unspecified. Where the form has been given the conventional Fick's Law was assumed. We wish to adapt the perhaps unsatisfactory procedure of drawing heavily upon results not yet published (Hearon, 1950b) in order to discuss a most interesting case. If one, following Onsager (1932, 1945), takes the $\vec{J}_k$ to be of the form

$$\vec{J}_k = \sum_j D_{kj} \nabla C_j \tag{64}$$

where D_{ii} is the conventional diffusion coefficient and D_{ij}, $i \neq j$, are the "drag coefficients," the equation of continuity becomes, for the steady state, in the cell

$$\sum_j D_{kj}^i \nabla^2 C_j^i = -q_k, \quad k = 1, 2, \cdots. \tag{65}$$

It has been assumed that the D_{kj}^i are essentially independent of concentration. Consider a spherical cell of radius r_0 in which the q_k are constant. The set (65) gives for the internal concentrations, C_k^i

$$C_k^i = -\frac{Q_k r^2}{6} + A_k, \quad k = 1, 2, \cdots, \tag{66}$$

where r is radius vector from the cell center, the A_k constants and the Q_k are for the case of *two* solutes,

$$\begin{aligned} -Q_1 &= (-q_1 D_{22}^i + q_2 D_{12}^i)/(D_{11}^i D_{22}^i - D_{12}^i D_{21}^i); \\ -Q_2 &= (-q_2 D_{11}^i + q_1 D_{21})/(D_{11}^i D_{22}^i - D_{12}^i D_{21}^i). \end{aligned} \tag{67}$$

The external concentrations C_k^e are given by

$$C_k^e = C_k^0 + B_k/r, \tag{68}$$

where C_k^0 is C_k^e at $r = \infty$ and

$$\begin{aligned} B_1 &= Q_1^e \frac{r_0^3}{3}, \\ B_2 &= Q_2^e \frac{r_0^3}{3}, \end{aligned} \tag{69}$$

where Q_k^e is the same function of the external coefficients D_{kj}^e that Q_k is of the D_{kj}^i. The A_k in (66) are given by

$$A_k = C_k^0 + Q_k^m \frac{r_0}{3} + Q_k \frac{r_0^2}{6} + Q_k^e \frac{r_0^2}{3}, \tag{70}$$

where Q_k^m is same function of the h_{kj} that Q_k is of the D_{kj}^i and the h_{kj} are *generalized permeabilities* having the same significance for flow across the membrane that the D_{kj}^i have for flow in the cell. For example the flow from the cell across the membrane of the first substance is

$$h_{11}(C_1^i - C_1^e)_0 + h_{12}(C_2^i - C_2^e)_0, \tag{71}$$

where the subscript zero denotes that the values are at $r = r_0$. A_2 is obtained from A_1 by interchanging the subscripts 1 and 2 everywhere in (70). Now let $q_1 = 0$ and q_2 be negative, corresponding to consumption in the cell of the second substance. Then

$$\begin{aligned} Q_1 &= -q_2 D_{12}^i/(D_{11}^i D_{22}^i - D_{12}^i D_{21}^i); \\ Q_2 &= \quad q_2 D_{11}/(D_{11}^i D_{22}^i - D_{12}^i D_{21}^i), \end{aligned} \tag{72}$$

and it can be shown from (66), (68), (69), (70) and (72) that the concentration of the first solute, C_1^i, though this solute is neither consumed nor produced, is everywhere higher in the cell than outside. It is in fact readily verified from (66) with (68), (67) and (70) that $C_1^i(r)$ is a paraboloid with its apex at the center of the cell. The distribution is formally identical with that (Rashevsky, 1948) of a solute which is being *produced* in the cell. The distribution C_1^i depends upon Q_1 from (72) in such a manner that the difference between $C_1^i(0)$ and $C_1^i(r_0)$ depends upon q_2 the rate of consumption of the second solute: If $|q_2|$ is increased the distribution changes so that C_1^i is even higher relative to C_1^e and the first solute flows *into* the cell *against a concentration gradient.* If the initial conditions are that at $t=0$, $C_1^i = C_1^0$ the "free energy of concentration" is given by, cf. (47),

$$\Delta F_{\text{conc.}} = 4\pi \int_0^{r_0} \mu_1 C_1^i r^2 \, dr - \frac{4}{3} \pi r_0^3 \mu_{10} C_1^0 , \tag{73}$$

where μ_{10} is the chemical potential of the first solute at the concentration C_1^0; μ_1 and C_1^i are to be expressed as a function of r from (32) and (66). Equation (73) gives the change in free energy *of the cell* accompanying the achievement of the steady state distribution from the initial distribution of the *first* solute. Similarly for two steady state distributions,

$$\Delta F_{\text{conc.}} = 4\pi \int_0^{r_0} \mu_{12} C_{12}^i r^2 \, dr - 4\pi \int_0^{r_0} \mu_{11} C_{11}^i r^2 \, dr \tag{74}$$

gives the "free energy of concentration" due to the first solute where μ_{11} and μ_{12} are the chemical potentials at any point r in the cell for the first and second steady state, a similar notation is used for C_{11}^i and C_{12}^i. Equations (73) and (74) give also the work which must be done upon the cell to effect such a change in distribution: It is easily seen that this is derived from free energy which would have been dissipated in the diffusion field of the second solute had the first solute not been present. From (66)

$$\begin{aligned} \nabla C_1^i \cdot \vec{r}/r &= -Q_1 r/3 ; \\ \nabla C_2^i \cdot \vec{r}/r &= -Q_2 r/3 . \end{aligned} \tag{75}$$

Taking Q_1 and Q_2 from (72) and $\vec{J}_k$ from (64) shows that

$$\vec{J}_1^i = \vec{J}_1^e = 0 . \tag{76}$$

Thus there is no net flow of the first solute and hence no dissipation in its diffusion field, though ∇C_1 is everywhere different from zero except at $r = \infty$. From (36) the rate of change of free energy due to diffusion, in the cell, of the second solute is

$$\frac{dF}{dt} = -\int_V \frac{R\,T\,D_{22}^i(\nabla C_2^i)^2}{C_2^i}\,dV - \int_V \frac{R\,T\,D_{21}^i\,\nabla C_1^i \cdot \nabla C_2^i}{C_2^i}\,dV. \quad (77)$$

In (77) the integrand of the first integral is positive, that of the second negative. The second integral is thus the deficit in *decrease* in free energy, per unit time, due to the presence of the first solute which is being maintained in a stationary distribution. The second integral is thus the "cost of maintenance" (free energy per unit time) of the non-equilibrium concentration distribution of the first solute. Thus one may say that (73) gives the "cost" of concentrating the first solute in the cell and the second integral in (77) gives the "cost" per unit time thereafter to maintain the configuration of C_1^i in the cell. It is not necessary that $q_1 = 0$ in the above but this simple case is clearest. It will be shown (1950b) that a similar situation holds for a cell producing or consuming any number of substances at any constant rates q_k. Cases will also be presented in which the q_k are neither constant nor independent. The above discussed situation is not offered as a "formal explanation" of anything. It does have these striking, if obvious, features: One meets the classical situation of a solute to which the membrane is freely permeable existing in higher concentration in the cell than in the environment. This is a non-equilibrium situation the existence and maintenance of which depends upon the metabolic state of the cell (substances being metabolized and the rates). If the metabolism of the cell is altered the non-equilibrium configuration is altered; in the extreme it vanishes if metabolism is stopped. This situation is a strict consequence of the laws of diffusion and requires no "one-sided" permeabilities, electrostatic forces etc. for explanation. It is *not* implied here that all such situations result from the laws of diffusion alone but the relevancy of the above remarks is plain.

Since the gradients in the above case are due to spontaneous chemical reaction in the cell one may by specifying the reactions compute under simple assumptions the efficiency of the use of "metabolic energy" for transport and concentration but this cannot be discussed here.

5. *General Remarks.*

It is not proposed to discuss here in detail the question of whether thermodynamics in the usual sense of the word is applicable to non-equilibrium systems and irreversible processes but a few remarks seem necessary. It is indeed true that thermodynamics is most frequently applied to such systems. Every calculation of ΔF from the familiar equation (12) of III is such a case. The term "equilibrium" as frequently used in thermodynamics does not imply a state such that the system left to itself will not change but a state describable in terms of *thermodynamic* or macroscopic variables (cf. discussion of LaMer et al, 1949). This may necessitate *thermal* and *mechanical* (but *not* chemical) equilibrium in the true sense of the word. For the system discussed in III there was assumed an assignable value of T and P for the *whole* system; if the mole numbers n_k can be prescribed the description is complete. If the mole numbers change *in such a way that they can be specified* at each stage of the process, the change in free energy can be calculated for *any* change and the time rate of change of the free energy (or any other function of state), cf. (1) and (6) of III, can be computed and there is nothing else to discuss. If T, P and C_k are not uniform in the system then the system must be divisible into parts in which these variables are uniform; these parts may be infinite in number, cf. (47), requiring a space integral for the complete description. Each element is in "equilibrium" in the sense that there are assignable values of T, P and C_k which obtain throughout the element. In extreme cases an adequate description may not be possible even by statistical methods but these are unusual systems. This latter point is well known and has been discussed by P. W. Bridgman (1941). The difficulties when they do arise are in general not associated with the fact that the system is changing at a finite rate but with such matters as the choice of suitable macroscopic variables and the difficulty of an *operational* definition of temperature as discussed by Tolman and Fine (1948). J. M. Reiner and S. Spiegelman (1945) in discussing Eckart's (1940b) equations give a completely misleading discussion (p. 81–82) implying that the formulations of thermodynamics are not available for irreversible processes. Their point of view is rather widespread. They further state that only inequalities are available from thermodynamics for the discussion of irreversible processes. That this is not correct is abundantly clear from section 1 of this paper, equation (6), and from Eckart's own work. They also, as a result of this point of view, fail to recognize the conclusions from (21) and (22) of III and (43) of this paper, which equivalent conclusions Eckart also proved in a different manner, and give an erroneous discussion (p. 91) of entropy increase and energetic coupling. A. Rosenbluth, N. Weiner, W. Pitts and J. Ramos (1948) have, most elegantly, stated that thermodynamics can be applied to systems near equilibrium and which change slowly but that to do so is an approximation. It appears to this writer that the approximation, as discussed above, must be that of describing the system and not associated with change *per se*, rapid or otherwise.

We hope not to have implied that there are no such problems to be met but the unfortunate stress of "equilibrium" and reversibility in connection with the applications of thermodynamics seems great enough to merit discussion.

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BOOK REVIEW

GEORGE BOOLE. *The Mathematical Analysis of Logic.* 1948. 82 pp. New York: Philosophical Library. (First published in 1847. Cambridge: Macmillan, Barclay, & Macmillan; London: George Bell.) $3.75.

The re-publication of George Boole's classical pamphlet, *The Mathematical Analysis of Logic* 101 years after its first appearance marks a recognition of the importance achieved by so-called "symbolic logic" in modern science.

The various applications of Boolean algebra or "logical calculus" of interest to mathematical biology should be familiar to the readers of this journal through the 1943 paper of McCulloch and Pitts and the subsequent development of the ideas embodied therein.

To this reviewer it seems that Boole's most significant contribution to science has been not so much through his invention of a particular logico-symbolic technique as through his emphasis on the symbolic nature of both logic and mathematics. It is this emphasis which brings out the inherent kinship of the two disciplines. Boole's voice was one of the first to declare clearly that it is not fruitful to define mathematics as the science of quantity or magnitude; that although mathematics does deal most effectively with magnitude, it need not be its sole subject matter. Today we would define the subject matter of mathematics as *structure,* and such a notion, although not yet explicitly stated, seems to inspire Boole's approach.

To those who are already familiar with the simple scheme of Boolean algebra, the most interesting part of Boole's book will be the Introduction. Two theses are defended there, (1) the fundamental unity of science and (2) the close relation between logic and mathematics. The implication of this orientation can be felt, namely, that the logicomathematical method is destined to be language of unified science. By a strange coincidence some of the most vociferous objections to this orientation came from Sir W. Hamilton, a logician bearing the same name as the scientist whose contributions to mathematical physics were enormous. Some older arguments against mathematicising knowledge are also taken up and disposed of. All of them reveal the ancient dichotomy between "how" and "why," which fortunately is now fairly thoroughly eliminated from science but unfortunately still lurks in undisinfected corners of philosophy.

One cannot, of course, reproach Boole, unaware as he was of modern semantics, that he failed to dispose of the dichotomy between "how" and "why" by subjecting it to operational analysis. Instead he did something else. He accepted the verdict of those philosophers who declared that since philosophy is concerned with "real existence" and the "research of causes," matters presumably too lofty to include logical analysis, therefore logical analysis forms no part of philosophy. In view of this verdict, George Boole concluded that it was justified for logic, exiled from the Elysian fields of philosophy, to seek refuge in mathematics.

And a very good refuge it turned out to be.

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